A Textbook of

MEDICINE

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CORONARY HEART DISEASE

Chapter 1

CLINICAL CORONARY HEART DISEASE AND CORONARY ARTERY ATHEROSCLEROSIS

Coronary heart disease is a clinical entity coronary athero sclerosis (or arteriosclerosis) a pathological entity A consider able body of scientific evidence links these two entities Yet much confused thinking is generated because of the failure to separate them and to realize their truly separate natures Indeed major elements of the progress made in the understanding of clinical coronary heart disease and its prevention have been pos sible only by a separation of the considerations of these two entities

CORONARY ARTERY ATHEROSCLEROSIS

The coronary arteries along with medium sized arteries elsewhere in the body are the seat of a disease process charac terized by a thickening of the intimal coat of the arterial wall The normal undiseased coronary artery has practically no tissue in the intimal layer between the endothelial lining and the inter nal elastic membrane The pathologic essence of the major dis ease process which affects the coronary arteries is an accumulation of inert material and tissue within this intimal coat internal to the internal elastic membrane Diverse chemical and structural elements are found to make up the material which accumulates within the intima of diseased coronary arteries Among these materials are lipids of various sorts calcium salts and even cal cium in the form of bone fibrous and fibro elastic tissue hemorrhagic areas and areas of thrombosis at various stages of organization

There exist several views concerning the pathogenetic sequence of events in the development of the mature arterial lesion. Largely such views differ with respect to the early stages of the development of the lesion and with respect to the structural feature considered as primary. One concept attributable to Rokitansky[1] and more recently to Duguid[2] is that thrombosis is the primary event in the artery and that the remaining morphologic features of the lesion are in some way a later result of such thrombosis. A second view originating with Winternitz, Thomas and Le Compte[3], holds that hemorrhage into the intimal part of the artery wall from vasa vasora is the primary process, all other features representing various aspects of the tissue reaction to such hemorrhage. A third view is centered around the lipid elements of the arteriosclerotic lesion. Anitschkow[4] proposed that lipids from the circulating blood infiltrate through the endothelial lining and there set up the original lipid deposits which initiate reactive changes on the part of the body with ultimate development of the full blown lesion. More recently there is the view of Rinehart and Moon that alterations in the mucopolysaccharide structure of the ground substance of the arterial wall is the initiating feature of the lesion and that the other aspects of the lesion are secondary to this. In support of each of these various views there are structural features and elements of biological evidence which suggest possible validity. Unfortunately, however, the proponents of each of the views concerning the primary materials which constitute the arteriosclerotic deposit have felt at times the necessity of insisting upon that primacy to the absolute exclusion of all other possibilities. What is worse, they have misinterpreted their privileges in this regard in that by insistence on a particular view of the primary structural element they have stated directly or indirectly that an entire body of biochemical, clinical and other evidence (which body of evidence is entirely self sufficient) must be incorrect. One is certainly entitled to entertain any view of the primary facets involved in development of the arteriosclerotic lesion. It is encouraging that various investigators have given much thought to possible modes of pathogenesis of this disease, but when such views are used to run head on into solidly established clinical and biochemical evidence, we reach an impass which is patently ridicu-

lous A view which is clearly in opposition with *facts* simply needs modification because it cannot be correct It may not be completely incorrect but it certainly needs modification

Perhaps a more fruitful approach to the entire problem is to recognize the existence of various structural features of the coronary arteriosclerotic lesion and to look forward to the time when an integrated concept of the origin and pathogenesis of this disease will allow for the proper placement of each such structural feature Insistence upon primacy of a particular feature at a time when such primacy cannot be established can serve only to impede progress which would otherwise be possible It is largely from considerations such as these that the author of this book prefers the term used by Goldblatt[6] to describe this lesion namely simple intimal arteriosclerosis rather than atherosclerosis In this way one eliminates the prejudicial view that the lipid element of the lesion is either primary or most important as is suggested by the origin of the term athero Many of the arterial lesions show very little lipid at that particular point in time when the pathologist has the opportunity to examine the tissue Unfortunately when such lesions are termed atherosclerotic lesions certain investigators take great offense because they can argue that there is no athero element to be found Such controversy can be eliminated by the use of the term simple intimal arteriosclerosis to encompass at this time those lesions which result in the accumulation of tissue or inert material between the internal elastic membrane and the lumen of the artery and which have the ultimate effect of narrowing the lumen of that artery

It is now fairly widely agreed as a result of careful pathological studies including the injection studies of gross specimens such as the classical ones of Blumgart and Schlesinger[7] the microscopic pathological studies of Spain and co-workers[8] and of Dry Edwards and White[9] that coronary arteriosclerosis *is* quantitatively related to the clinical manifestations of coronary heart disease In Blumgart and Schlesinger s very beautiful injection studies it was clearly shown that in the presence of clinical coronary heart disease in the form of angina pectoris or myocardial infarction the coronary arteries at post mortem examination show extensive arteriosclerosis a degree of arteriosclerosis definitely *in excess* of that found in

patients without such clinical disease This is so despite the fact that essentially all so-called healthy individuals show some degree (and often a marked degree) of coronary arteriosclerosis The important issue is not that the apparently healthy individuals do show *some* coronary arteriosclerosis but rather that they show a lesser extent of this process on the average than do those individuals with overt clinical coronary heart disease In a careful study of post mortem material from individuals dying in the age range from 20 40 years of age Spain showed clearly that the average degree of narrowing of the coronary arteries due to accumulation of arteriosclerotic tissue in the intima was very much greater in individuals who died of myocardial infarction than in those who died accidentally of a variety of causes other than clinical heart disease

The studies of Dry Edwards and White provided similar findings of an excessive degree of coronary arteriosclerosis in persons with clinically manifest coronary heart disease None of these findings call for an insistence that every case of clinical coronary heart disease either in the form of angina pectoris coronary insufficiency or myocardial infarction necessarily rests upon an etiology of coronary arteriosclerosis although it is quite clear that the vast majority of such cases are significantly associated with coronary arteriosclerosis Some authors have considered coronary arteriosclerosis to be the etiology of as many as 95 per cent of cases of clinical coronary heart disease while others have suggested somewhat lower percentages than this Other possible pathological bases for clinical coronary heart disease have involved such features as (1) rheumatic or syphilitic involvement of the coronary artery ostia (2) anomalous origin of one or more of the coronary arteries as from the pulmonary arteries and (3) anomalous congenital stenotic lesions of the coronary arteries This entire latter group of possibilities is regarded in present day coronary heart disease material not to constitute anything more than perhaps 10 per cent of the total basis for clinical coronary heart disease Thus it seems quite clear that coronary arteriosclerosis is the major underlying lesion present in the arteries related to the development of clinical coronary heart disease However this fact has created a certain amount of confusion in

the mind of certain investigators who doubt the etiologic significance of coronary arteriosclerosis and who misunderstand its relationship with the clinical disease One such misconception is that which centers around the widespread occurrence of coronary arteriosclerosis in the adult population of a country like the United States

It is perfectly true that if one were to examine the coronary arteries of a large group of 50 year old United States males in health one would find an appreciable average involvement of such arteries with arteriosclerosis Indeed some of the individuals in apparent health will show a greater degree of coronary artery arteriosclerosis and attendant narrowing than will certain individuals of the same age and sex who have suffered one two three or even four myocardial infarctions An erroneous conclusion that has been drawn by some is that coronary arteriosclerosis cannot be very important if individuals in apparent health can have at times more coronary arteriosclerosis than individuals who have overt clinical coronary heart disease We do know now that on the average the degree of coronary arteriosclerosis is higher in individuals with clinical coronary heart disease than it is in otherwise comparable individuals without clinical coronary heart disease But what we must realize urgently is that individuals who are in apparent health today are fully entitled to show varying degrees of coronary arteriosclerosis some very extensive degrees some moderate degrees and some *minimal* degrees This in no way contradicts the relationship of coronary arteriosclerosis with the clinical entity coronary heart disease

First it is important to realize that the individuals *in apparent health today* at age 50 years represent the prime substrate out of which grow the individuals who later become labelled individuals with overt clinical coronary heart disease Certainly if coronary arteriosclerosis is etiologically related to clinical coronary heart disease it is essential that many so-called healthy individuals must be developing coronary arteriosclerosis for otherwise we would never see any *new* cases of clinical coronary heart disease This latter is unfortunately not the case inasmuch as the clinical entity continues to develop in alarming proportions in our population every day The true nature of the

relationship of coronary arteriosclerosis and clinical coronary heart disease is really that with an increasing average degree of coronary arteriosclerosis the *risk* of a clinical manifestation such as angina pectoris coronary insufficiency, myocardial infarction or heart failure becomes progressively greater It is important to underline that this is a *risk* of such a clinical event becoming greater It is *not* an absolute certainty nor is it an absolute certainty *in any specified time interval* The matter might be put this way If one were able to segregate two groups of individuals in the population both groups being in apparent health with one group showing an extensive degree on the average of coronary arteriosclerosis and the other showing a minimal average *degree of coronary arteriosclerosis and then could follow* both groups for some time period e g one month one year or ten years the following would be true There would be more cases of clinical coronary heart disease appearing in the group with extensive coronary arteriosclerosis than there would be in the group with minimal coronary arteriosclerosis Furthermore the wider the separation in average degree of coronary arteriosclerosis between the two groups the wider will be the disparity in numbers of individuals who develop a clinical manifestation of coronary heart disease in any particular time period

Precisely why it is that one individual with a particular degree of coronary arteriosclerotic involvement has a clinical episode at some period in life and another avoids such an episode for some extended period beyond that is not at all clear at the present moment It is entirely possible that this will not be clear for many many years to come Speculation is of course easy as to possible reasons for the sudden transformation from the sub clinical state to the clinically overt state of coronary disease For example the occurrence of thrombosis superimposed upon an arteriosclerotic area occurring over a period of hours and days can effect this transformation The occurrence of intimal hemorrhage into an atheromatous plaque and the changes attendant upon this can suddenly decrease blood supply critically to a region of the myocardium and produce clinical manifestations In addition physiologic factors operating in an individual with narrowed coronary arteries can conceivably be immedi

ate provoking factors The extent to which such factors as functional vascular spasm are operative is not clear but one should not rule out their possible importance One issue must remain uppermost in the mind of the physician dealing with the problem of coronary heart disease in a preventive manner namely that with increase in the degree of arteriosclerotic narrowing the risk of a clinical episode rises progressively This is so even though no date can be assigned to such an episode nor may we know what immediate factor will precipitate the clinical episode In problems such as these it is often worthwhile to reflect upon our medical objective In this case our objective is the prevention of *clinical* coronary heart disease While understanding of every last facet of the physio pathology of the evolution of coronary heart disease is a most desirable and laudable aim this should never be allowed to interfere with efforts to reduce mortality as soon as possible whether or not the entire physio-pathology is understood The entire body of evidence on this subject would indicate that if coronary arteriosclerosis could be minimized the incidence of and mortality from clinical coronary heart disease would also be markedly reduced This is the essential issue here That confusion on this issue is rife in high places can best be illustrated by citing certain important studies which have attempted to cast doubt on the importance of coronary arteriosclerosis for clinical coronary heart disease In one such study Morris[10] has obtained data from pathological records in one large London hospital where he felt the pathological grading scheme was sufficiently similar throughout a period of 40 years to enable him to estimate whether coronary arteriosclerosis exhibited a rising trend a falling trend and or no change over this time period His finding in the material at his disposal from autopsy records was that coronary arteriosclerosis appears to have decreased in average degree over this 40 year span in England However during that same span of years the vital statistics for England showed that there appeared to exist a real and striking increase in the incidence of clinical coronary heart disease and in mortality therefrom even after correction for medical awareness of the disease and for improvement in diagnostic methods When such a situation arises there are several

possibilities that must come into consideration. But one point both of philosophical and scientific consequence must first be emphasized. Whatever possibilities are invoked to explain the paradoxical findings, they can hardly be correct if they flout directly other existing well established observational data. At any time the existing *interpretation* of solidly established observational data may require revision, even radical revision, but new facts brought to light on an issue cannot negate *facts* which have also been proven to be as solidly established. Some of the possible explanations of the observations of Morris concerning the apparently opposite trends in coronary arteriosclerosis in England and those in clinical coronary heart disease mortality are the following:

First. Is the pathological grading that has been used *really on a constant basis such that one can use the reports of pathologists* of even one hospital over a 40 year period for this type of analysis?

Second. Is the clinical material of the Guy's Hospital on which these conclusions are based really representative of the trends in the British population at large? With respect to this issue one might appreciate better assurance of the representative character of such hospital material. Physicians are well aware that numerous factors, even some over and above the type of illness which results in hospitalization of particular types of patients, can change markedly from one decade to the next. Indeed, they can even change from one year to the next depending upon the introduction of new therapeutic and diagnostic tools. The issue of comparability of hospital material over a 40 year period in a particular London hospital is a real and major one.

Third. One may assume that the possible objections inherent in the first and second questions raised above are not valid *and that the data are as they seem to be. Then the problem* can be stated: Are these the only data we have on this subject or are there other? In the text above are very crucial solidly established experimental data relating coronary arteriosclerosis to clinical coronary heart disease. Hence, we are not operating in a vacuum with respect to this problem, for we have excellent direct evidence that coronary arteriosclerosis is indeed related to

clinical coronary heart disease No data accumulated by Morris or by others concerning arteriosclerosis trends over 40 years in London hospitals or coronary heart disease mortality in Britain over that same time period can possibly negate these well established relationships If the observations detailed by Morris are truly correct as they stand there must be some rational way to bring them into harmony with the known well-confirmed relationship of coronary arteriosclerosis and clinical coronary heart disease We know well that we do not understand all the factors that convert a sub-clinical case of coronary arteriosclerosis into a case of clinical coronary heart disease This has just been alluded to repeatedly Therefore it would be very pertinent for us to inquire whether one or more of the factors that determine the conversion of coronary arteriosclerosis at the sub-clinical level into clinical coronary heart disease might not have undergone alteration in this 40 year period in England and thus be responsible for the trends observed Indeed with this approach one might hope that the resolution of this apparent paradox would add additional understanding to the entire problem of coronary heart disease rather than serve merely to confuse the issues For some reason the type of data uncovered by Morris has been used by some authors and some so-called authorities on coronary disease as evidence refuting completely a host of other relationships such as the relationship of pathologic to clinical findings such as the biochemical relationship of blood lipids with coronary heart disease and still others These last mentioned relationships can in no way be contested by the type of evidence which Morris has presented since the relationships stand on their own merits It is indeed discouraging with respect to the progress in understanding disease that data such as those of Morris are misinterpreted and misused

Other aspects of the relationship of coronary arteriosclerosis with clinical coronary heart disease have been equally misunderstood and misused with the result of adding confusion A cardinal one that deserves discussion is that of the relationship between coronary artery disease in the male and the female of the human species both with respect to the pathological features of coronary arteriosclerosis and with respect to the occurrence of

clinical coronary heart disease The best available data indicate that the following is true for young men and young women, for example in the 30 39 year age decade (1) there is on the average, a greater degree of involvement of the coronary arteries with artriosclerotic narrowing in the men of this age group than there is in the women (2) There is a much greater incidence of the occurrence of clinical coronary heart disease in men of this age group than in women The exact extent to which the incidence in men exceeds that in women has been estimated to be anywhere from two fold to twenty fold depending upon the authority quoted Many of the authoritative comments on this subject are based upon material with a variety of biasses built in and hence can be disregarded entirely It does appear however from vital statistics information that probably the correct order of magnitude of this factor of difference is about 4 or 5 that is men in this age decade have about 4 or 5 times as great an incidence of clinical coronary heart disease and death therefrom as do *women in this same age decade On the other hand* the difference in the average degree of coronary arteriosclerosis between men and women of this age decade is by no means a 4 or 5 fold difference It is a very much smaller difference Some *authorities have concluded that since the incidence* of clinical coronary heart disease is about 4 or 5 times as great in the male as it is in the female but since the difference in degree of coronary arteriosclerosis is very much less than this there must exist some reason why males are so much more susceptible to coronary heart disease than females other than the factor of coronary arteriosclerosis This type of argument is based on the *assumption* that if the clinical incidence of coronary heart disease is 5 times as great the amount of arteriosclerosis must necessarily be 5 times as great in men than in women A search of any of the elements of simple logic a search of the literature or any other available source will reveal no evidence whatever for the expectation that the difference in degree of coronary artriosclerosis between men and women must be 4 or 5 fold if the difference in clinical disease incidence is 4 or 5 fold No one has ever shown that these two related phenomena must necessarily be associated by a straight line relationship Indeed a variety of

biological phenomena physical phenomena and others are known not to be related in this linear way A simple analogy would be that between the radius of a circle and the area of a circle If the radius of a circle is doubled the area is increased four fold It is highly unlikely that anyone measuring the area of circles of these two radii would express surprise that the area of the circle drawn from a radius twice as large as that of the first circle is found to be four times as much instead of two times as much Why surprise is expressed concerning the absence of a linear relationship of coronary arteriosclerosis with clinical coronary heart disease is not at all clear except insofar as it is a manifestation of loose scientific thinking It should *occasion no* surprise if the final evolution of the facts would indicate that a *ten per cent increase* in degree of arteriosclerosis above a particular value might result in a two fold four fold or even six fold increase in the risk rate of an attack of clinical coronary heart disease This may very well turn out to be the case Such variables need not be associated in a straight line relationship Were this simply a matter of erroneous thinking with no consequences one would hardly need to labor the point further But the absence of the *straight line* relationship between coronary arteriosclerosis and clinical coronary heart disease incidence has led some persons to state that the two phenomena must not be related at all although all the evidence clearly *proves that they* are Also and perhaps more damaging it has led to the concept that since coronary arteriosclerosis is not adequate to explain the difference in incidence of clinical coronary heart disease between the male and female it is necessary to look for some other factor of explanation As a result of such erroneously based thinking vast research projects can be initiated to uncover this hypothetical other factor which it *is deemed* necessary to discover to account for the male female difference It is not the intent here to state that no other factor could possibly exist but rather to state very clearly and unequivocally that if fallacious reasoning leads to a search for some other factor presumed to be necessary then such a search may very well be a wild goose chase leading to a non existent pot of gold at the end of the rainbow

There is another major area where misunderstanding of

the relationship between coronary arteriosclerosis and clinical coronary heart disease has delayed adequate progress with respect to the practical aspects of management of this disease It is a very well known fact to every physician that no method exists at the present time for an anatomical or microscopic examination of the coronary arteries during life to determine the exact degree to which they have been narrowed by arteriosclerosis Nor does there exist any other technique which will enable one to assess the exact degree of such arteriosclerosis For inexplicable rea sons statements repeatedly appear in the medical literature to the effect that since no method exists for measuring the degree of coronary arteriosclerosis during life there is nothing that can be done with the problem of *clinical* coronary heart disease until such measurements are available No scientific evidence can be marshalled to support such a statement If certain biochemical and physiologic variables can be quantitatively related to the in cidence of clinical coronary heart disease our inability to meas ure *the degree of coronary arteriosclerosis in life simply has* nothing whatever to do with prosecution of any of the leads that arise out of the measured relationship between the biochemical and physiologic variables and the phenomenon of clinical coro nary heart disease This important issue can be further illus trated by taking an extreme point of view Let us assume (even though the assumption is false) that arteriosclerosis of the coro nary arteries had nothing whatever to do with clinical coronary heart disease There still would exist every reason to go forward rapidly with the study of bio chemical and physiological variables in relation to the clinical entity even without knowing the under *lying pathology at all This is not to say that knowledge of the* underlying pathology and the relationship of bio-chemistry to the pathology as well as to the clinical entity is not desirable Of course it is an ultimate goal sought by all students of this dis ease An excellent illustration of the danger of impediment to practical progress with management of coronary heart disease arising out of the erroneous impression that we must wait for a *method of measurement* of coronary arteriosclerosis during life is available in the field of the relationship of blood lipids with coronary arteriosclerosis and clinical coronary heart disease This

relationship itself will be elaborated on in detail in subsequent chapters At this point it is sufficient to state that a strong relationship exists between blood lipids in the form of lipoproteins and clinical coronary heart disease

Those who argue the immediate need to be able to measure the exact degree of coronary arteriosclerosis in life say Since the blood lipids operate via an effect on degree of coronary arteriosclerosis and since we cannot measure exactly how much coronary arteriosclerosis there is in life how can we possibly apply the blood lipid findings clinically? The answer to this is that the blood lipid findings have been developed in relationship with *clinical* coronary heart disease They do not rely in any way for support upon any findings having to do with coronary arteriosclerosis Neither is the utility of this relationship in the practical management of prevention and treatment of clinical coronary heart disease in any way dependent upon a relationship of the blood lipids with coronary arteriosclerosis or upon any hypotheses concerning such a relationship It is true that most workers who have studied this problem feel the evidence is extremely strong that the relationship of blood lipids with clinical coronary heart disease does arise via the intermediacy of coronary arteriosclerosis but this is in no way necessary Should it turn out in the future that the blood lipids are in no way related to coronary arteriosclerosis the well established relationship with clinical coronary heart disease would be just as useful and just as applicable in the problem of prevention and management of coronary heart disease Ultimately of course one would like to know the interrelationship of all these measures and entities but it is very important not to confuse *supposed* dependency upon one unmeasurable variable with the ability to go ahead with the problem at the clinical level Therefore the inability to measure degree of coronary arteriosclerosis in the living person need not in any way be a stumbling block to progress with the practical problem of prevention or treatment of clinical coronary heart disease It is in an area such as this that it is extremely important to differentiate clearly what is meant in discussing coronary arteriosclerosis and what is meant in discussing clinical coronary heart disease

From the point of view of the physician interested in trying to prevent clinical heart disease from the point of view of the intelligent layman who would like to avoid coronary heart disease interest centers in the *clinical* entity of coronary heart disease in manifestations such as myocardial infarction angina pectoris arrhythmias heart failure and death The interest is not primarily in the pathological process underlying such clinical states To be sure where understanding of the pathology could assist with the management of the problem at the clinical level such understanding is greatly to be welcomed However since the essence of the problem at the practising physician s level is clinical coronary heart disease rather than pathology it is the intention of the author of this book to develop completely in the ensuing chapters the concepts of interest for clinical coronary heart disease without any *dependence* whatever upon concepts of coronary arteriosclerosis Where it is felt that coronary arteriosclerosis represents the mechanism by which a given effect is mediated comments will be made to so indicate but in no case will the development of the ideas and the application of such ideas be in any way dependent either upon facts or concepts concerning coronary arteriosclerosis Rather the intent is to develop for the physician reader what we know about the evolution of coronary heart disease as a clinical entity what can be done about its advance prediction and what can be done about its prevention and management without any dependence upon its inter relationship with coronary arteriosclerosis

Chapter II

IDENTIFICATION OF FACTORS IN THE DEVELOPMENT OF CORONARY HEART DISEASE

The sub clinical phase of coronary heart disease is that upon which major interest must center for real effectiveness in the prevention of the clinical disease *Prevention* of clinical coronary heart disease appears to have more attractive prospects than does treatment of acute clinical episodes when they arise By the very nature of the statement that coronary heart disease is sub-clinical during that period when its recognition is most urgent the inference is made that it will be necessary to develop some means of identification for *individuals* which will determine the status with respect to sub-clinical coronary heart disease Stated alternatively an endeavor is necessary to develop variables that can be measured which will provide some way of rating a person on a scale of risk with respect to his future prospects of evolving from the sub-clinical phase into the phase which must be avoided namely the phase of clinically manifest coronary heart disease In such an endeavor one would be perfectly justified in considering any possible measurement that can be made in people where the term might refer to measurements in the area of anatomy of physiology of biochemistry of psyche of family traits of environment or even still other areas It could not be predicted in advance in a totally new problem from which of these areas the significant information might arise If no information is available on this problem one can simply screen measurement after measurement to determine whether or not any provide information concerning either the rate at which sub-clinical coronary heart disease is developing or its total extent Quite obviously such a screening procedure could be extremely lengthy before

any variables of consequence are uncovered. Unfortunately this may be necessary in certain problems. In others there exist some available clues *suggesting profitable* directions of investigation. At times such clues may have arisen from animal experimentation. At other times they may have arisen through the practical clinical experience which has been accumulated over a period of years and suggests that one or another factor might be of importance. In the absence of either of these sources of possible leads to avoid the massive screening procedure one might, from a knowledge of the pathology of a disease or from some wholly *other facet, such as the inter-relationship* between two diseases, get some idea of a profitable area in which to seek clues rather than to screen every possible area.

It is worth comment here upon the nature of measurements that can be made. Measurements fall into various categories depending upon the precision and accuracy with which they can be made. For example, with respect to the height of a man, one could measure this quite accurately and there would be no reason *not to do so. On the other hand, with respect to some other* factors characterizing an individual, one might be quite satisfied to be able to grade individuals into four classes, such as zero, plus one, plus two, plus three and plus four. There is nothing wrong with either type of measurement. It is self-evident that where a measurement can be refined, it will in general be more useful in assessment of a trait of interest. However, under certain circumstances, where a particular measurement is quite variable *in an individual from day to day or hour to hour,* it would hardly be worthwhile expending too great an effort in obtaining great precision on any single measurement, since such precision is not warranted because of the variation with time. A pre-requisite of any feature to be measured in individuals is that the feature be different in extent in those persons developing sub-clinical coronary heart disease at a high rate compared with those developing the disease at a moderate rate and different to an even greater extent *from those developing the disease at a low rate.* It does not matter whether the measurement is *lower* in those developing the disease more rapidly than in those not developing the disease rapidly or whether it is *higher.* In either event the

measurement will be useful for the present purposes Next it is essential that the measurement which is different for those developing coronary heart disease rapidly from those developing it at a lesser rate must be different *early enough* in the sub clinical phase of the disease to be useful This requirement deserves an illustration For example if there were a measurement related to coronary heart disease that became abnormally high or abnormally low in the couple of hours or couple of days preceding a myocardial infarction such a measurement would be of very little use with respect to minimizing the rate of development of sub-clinical coronary heart disease which goes on for a period of years and decades To be really useful the measurement must be abnormal early in the period of sub clinical development of the disease which means it must characterize the individual years if possible before the occurrence of a clinical manifestation of coronary heart disease such as myocardial infarction

Another very important feature to be determined for each such measurement is the extent to which that measurement provides new additional information concerning the problem at hand in this case the rate of development of sub clinical coronary heart disease It is entirely possible that in approaching a problem such as coronary heart disease one might find that not only is there one measurement of importance but there are as many as five or more measurements that can be shown to have some relationship to the rate at which sub-clinical coronary heart disease is developing In the event that multiple measurements seem valid it is of prime importance to determine whether or not all the measurements provide what may be called *independent* or truly new information If each measurement does provide independent information then it is necessary to measure each in order to obtain the best assessment of the rating of a particular person with respect to sub-clinical coronary heart disease If the measurements do not all provide independent information then the measurement of any which do not provide *independent* information is superfluous confusing and a waste of time Let us consider a specific illustration concerning this feature of independence utilizing some factors for which evi

dence exists of a relationship with the rate of development of sub clinical coronary heart disease These are the blood lipid level and a family history of early clinical coronary heart disease Do these two factors provide independent information that can be used to assess a person s status with respect to coronary heart disease at the sub clinical level? Assume that family history of coronary heart disease can be rated on a measuring scale from zero through plus 4 depending upon the frequency of occurrence of early coronary heart disease in parents and other relatives of the individual It is known (to be developed in detail later) that blood lipid levels are related to the rate of development of sub clinical coronary heart disease the higher the blood lipid level the greater the rate of development of sub clinical coronary heart disease In the absence of other information it is possible that the availability both of the family history rating and the blood lipid level may provide much more information than either one alone However it is *not necessarily* true that availability of both types of measurement allows a better assessment of the heart disease risk in an individual under study In order for the two types of measurement to provide more information than either one alone, they must provide independent information in other words information concerning factors in development of coronary heart disease that are at least in part really basically different from each other It might be imagined for example that a family history of early coronary heart disease could operate in one of several possible ways such as inheritance of an anatomically peculiar coronary vascular tree that either favors poor nutrition of the heart muscle or predisposes to narrowing of the arteries by some mechanism or inheritance of a variety of other possible anatomical or physiologic features affecting the coronary arteries or the heart itself On the other hand the unfavorable family history might conceivably reflect a predisposition on a hereditary or familial basis to the development of elevated blood lipid levels It should be evident that if the family history operates only by influencing the chance that the person would have an elevated blood lipid level the family history is then providing nothing additional to the information directly available in a blood lipid measurement Indeed under such circum

stances the family history would at best be providing far more crude information concerning the blood lipid levels than blood lipid measurement itself In such a case one would consider that the family history provides no independent information and hence that a rating on a family history basis would contribute nothing new if the blood lipid levels are available On the other hand if it should turn out that the family history really operates via some mechanism such as inheritance of a poor coronary vascular tree anatomically then the situation is an entirely different one In this event the family history does provide additional independent information and hence an individual s risk of development of coronary heart disease is much better assessed if both the family history and blood lipid measurements are available than with either measurement alone Another way of presenting the problem of independence of information would be along these lines Assume that several factors were measurable and proven to be associated with the development of coronary heart disease Assume further that two individuals had the same value of each such factor If now a new measure becomes available and the two individuals differ on this measurement then is the risk of coronary heart disease higher in one of the individuals than the other? If the risk is higher the new measure does provide independent information and should definitely be added to the battery of evaluation tests This is essentially the scientific basis for testing independence of information provided by measurements There exist excellent statistical methods for checking the issue of independence such methods being based in essence upon the procedure of making all but one factor out of a set of factors equal and then testing for the association of the remaining single factor with the disease in question When by such a careful statistical test the one factor still seems related to coronary heart disease it can be inferred that statistical independence has been demonstrated Such demonstrations of statistical independence or demonstrated Such demonstration of statistical independence or respect to coronary heart disease is very far from an academic matter First of all it is of tremendous importance with respect to guiding further research efforts with respect to the disease Second at the practical clinical level it can help avoid duplication

of effort and of tests and indeed can help avoid erroneous and serious mis diagnosis and mis prognosis of the future of some individuals Thus returning to the illustration of family history and blood lipids let us assume that by the statistical test methods referred to above it has been demonstrated that the blood lipids are important but that the family history is of importance only because on *the average the blood lipids are higher in those families* where coronary heart disease has occurred excessively In this case there is no independent information in the family history Now if a clinician dealing with a particular patient does not realize this fact he can make errors in either of two directions First in a patient whose blood lipid status and whose family history are known and in whom the blood lipid status is excellent but the family history is poor this physician, not realizing the lack of independent information in the family history might erroneously be concerned about the unfavorable family history The correct point of view in such a situation is that even though *on the average the blood lipids may be worse in persons with a* bad family history of coronary heart disease this particular patient seems to have escaped the blood lipid defect and need have no fear whatever concerning the poor family history of coronary heart disease with respect to his own outlook for development of this disease The error that can be committed on the other side occurs in the case of a person who has an excellent family history of longevity and freedom from coronary heart disease but where the person has extremely high blood lipid values The extremely high blood lipid values would indicate a high risk of future clinical coronary heart disease and a high rate of development *of the entity of sub clinical coronary heart disease* The prognosis is therefore unfavorable If the physician assumes in such a case that the patient has nothing to fear because he has such an excellent family history of freedom from coronary heart disease he would be giving the patient a very false sense of security unjustified by the facts This might even prevent the patient from taking necessary measures which would reduce his high risk *of future coronary heart disease* These illustrations are presented primarily to point up the intense practical clinical importance of knowing whether or not the various factors meas

ured truly provide information of independent character There is one special situation that must be considered before too casual a dismissal of the independent importance of a particular factor with respect to coronary heart disease A particular factor that is known to be associated with coronary heart disease may make its effects manifest at one period of life whereas it does not do so at some other period in life Let us return again to the illustration concerning blood lipids and family history of coronary heart disease In testing for independence of family history of coronary heart disease and blood lipids one would apply the types of technique discussed above However the possibility has to be considered in this situation that the nature of the familial factor is such that it makes itself manifest for example at some relatively later period in life than early adulthood One might consider the possibility that a poor family history *is associated* with a predisposition to poor blood lipid control but that this predisposition does not become manifest in the average person until 35 or 40 years of age If an individual at 30 years of age is under consideration and if his blood lipids are found to be favorable but his family history poor the finding of the favorable blood lipid pattern at age 30 years would lead by too casual dismissal of the family history to the concept that family history is unimportant for this individual However if the familial predisposition is of a type becoming manifest between 35 and 40 years of age the family history should not be dismissed Instead in this type of individual with favorable blood lipids at 30 years of age the family history should put the physician on notice that the future blood lipid status of this patient should be watched In this hypothetical illustration though the family history is operating via an effect upon blood lipids it is providing independent information in that it tells us that the blood lipids may become abnormal *in* this person at some later time in life whereas this might not be the case in the population at large without this particular familial predisposition This might be regarded as an illustration of *semi independent* information and hence information that should not be disregarded Probably this type of situation arises relatively infrequently Nevertheless we know that it can arise and should be borne in mind in evalua

tion of the approach to factors involved in a disease such as coronary heart disease

In summary our goal is to identify each and every factor if there are indeed multiple factors, which provide independent *information concerning the outlook for the development of sub clinical and ultimate clinical coronary heart disease* For if these independent factors can be identified we can make the best *composite assessment of a person s status* and further can utilize the possibility of a multi faceted approach to prevention of heart disease in an individual And the possibility of a multi faceted approach needs to be considered If there is *only one* factor involved then there is no indication for a multi faceted approach On the other hand if multiple independent factors really do exist they must of course all be given attention There may exist a difference in the ease with which one factor or another can be brought under control and it would certainly accrue to the patient s benefit to control those factors readily controllable than not to manage any of them effectively Of course where multiple factors exist control of all can be anticipated to produce the best clinical results in reduction of risk of heart disease

The entire issue of independence of factors involved in the development of coronary heart disease is of great pertinence to the research worker as well as to the practising clinician From clinical evidence from epidemiologic studies from endocrine studies and from a variety of other sources new information possibly pertinent for the problem of coronary heart disease has arisen and will arise in the future It is urgent that when such new information arises the first question to be asked is Does this really provide *new* independent information in terms of factors that are related to the development of clinical coronary heart disease? This does not infer that the information itself is not new but rather the question is being raised here as to whether the information is but another reflection of some factor which we already know about and concerning which cognizance is already taken As an illustration it may be assumed that new research suggests that the level of a particular hormone is either lower or higher in those individuals developing sub-clinical coro nary heart disease at an excessive rate Assuming that this find

ing had never been made before it is obviously a new finding Indeed it may be a finding of tremendous importance in our understanding of the disease as well as in our handling of it but it is of prime urgency to know how this hormone level operates For example if the particular hormone under consideration operates as one factor in the control of the level of blood lipids it is vital that this be realized For there would be no virtue in attempting to alter that hormone level if the particular patient already has favorable blood lipid values In this type of situation the purpose of an effort to alter the level of this hormone would be only to attempt to achieve an improvement of the blood lipid level This in no way minimizes the importance of the particular hormone but it may save the patient and physician needless effort to alter something of no consequence of and for itself If for example one already were able to alter the blood lipid level very favorably by simple methods not involving this particular hormone it would follow that there is no additional benefit conferred upon the patient by the alteration of the particular hormone system for itself In the problem of coronary heart disease as with other problems of this type in medicine we must endeavor to achieve a reduction to simplest terms consistent with the reality of the situation If the simplest terms involve the consideration of ten separate independent factors we have no choice but to deal with all ten On the other hand if the simplest terms involve one or two factors it is confusing and a waste of effort to retain eight or nine additional duplicative factors that truly have no independent position with respect to acceleration of the disease process under consideration

THE IDENTIFICATION OF INDEPENDENT FACTORS ASSOCIATED WITH THE DEVELOPMENT OF SUB CLINICAL CORONARY HEART DISEASE

It was stated above that in a new problem one could approach the search for factors related to the development of the disease by screening processes screening every possible anatomical physiological and biochemical value or one could alternatively utilize leads that arise through a variety of sources In the case of coro

nary heart disease we have been abundantly presented with leads suggesting factors to be investigated It may be pertinent at this point to list some of the numerous leads that investigators of the *problem of coronary heart disease* have had available to them and the sources from which these leads came It is of interest to remark however that the entire list of leads have so far produced only two factors that appear to be independent ones related to the acceleration of development of coronary heart disease at the sub-clinical level At the present time all the others seem very likely to be related to one or another or to both of these two factors

These leads are listed below

(1) The greater frequency of occurrence of episodes of clinical coronary heart disease with increasing chronological age

(2) *The greater frequency of occurrence of clinical* coronary heart disease in the male of the human species as compared with the female especially at relatively young ages

(3) The occurrence of excessive and premature coronary heart disease in certain families characterized by blood lipid disturbance

(4) The occurrence of premature coronary heart disease in diabetics at least in the pre insulin era and the transition era

(5) The similarity of the blood lipids to those in the arteriosclerotic plaques of the coronary artery

(6) The induction of arteriosclerosis by cholesterol feeding in a variety of animals

(7) The difference in geographic incidence of coronary heart disease as determined by epidemiologic studies

(8) The implication of the diet of certain peoples in development of coronary heart disease

(9) The change in incidence of coronary heart disease during privation as in war years and post war periods

(10) The frequent association of coronary heart disease with hypertensive disease

(11) The occurrence of excessive arteriosclerosis in areas of the vascular tree subjected to excessive pressure

(12) The excessive incidence of coronary heart disease in cigarette smokers

(13) The excessive heart disease mortality in over weight persons

(14) The widespread opinion that a family history of excessive vascular disease is a predisposing factor to coronary heart disease

(15) The rising trends in mortality from coronary heart disease in the past half century in Western civilization

(16) The striking relationship of xanthomatosis with coronary heart disease

(17) The association of coronary heart disease with certain other diseases such as nephrosis and myxedema

(18) The difference in coronary disease incidence for various occupational categories

If coronary heart disease truly had some 15 to 20 independent factors involved in its development the medical task of prevention and management would certainly be complicated and difficult But 15 or 20 clues do not necessarily mean the existence of 15 to 20 independent factors in the disease The first step is a determination of the validity of the information in the clue Next valid information derived from each clue must be assessed for its independence At the present time of all these clues and suggestions concerning coronary heart disease two major factors have stood the test of careful analysis as being capable of providing valid *independent* information about the development of subclinical coronary heart disease and of course of ultimate clinical coronary heart disease All the others appear to derive validity through a relationship with one or another of these two factors or with both Therefore the considerations immediately ahead deal with these two factors The later chapters of this book will deal with the relationship of the other clues and suggestions to these two factors It is not meant that the two factors to be described here are the only two that will ever be discovered to have independent status or that other factors are either not valid or of importance Validity and importance are issues of a different type from that of independence of information

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highly recommended and while the findings derived therefrom often provide excellent leads for study of the human problem the ultimate evidence with respect to blood lipids or any other factor must be derived *in the human population* directly We must remain cognizant of the marked differences in the various animal species and of the possibility that what is important for one animal species may not hold for another Indeed what may be important for *several* lower animal species may not hold for the human Therefore while no thought should be given to the idea of deprecating results on coronary disease in the chicken the rabbit or the dog it is still true that our interest is coronary heart disease in the human Therefore any findings that must go into the day to day practice of clinical medicine in the effort to prevent coronary heart disease must have been proven valid for the human This generalization holds for blood lipids or any other factor of interest

How is the problem approached of demonstrating whether or not a factor such as the blood lipid level is associated with the development of coronary heart disease? Secondly and beyond the question of association is the measurement of blood lipids of practical clinical utility in determination of the rate of progression of sub clinical coronary heart disease and hence in prediction of the most likely candidates for future clinically manifest coronary disease? Even though some of the clues that lead to the study of blood lipids arise out of pathological considerations of coronary arteriosclerosis the development of the evidence concerning blood lipids in clinical heart disease can and will be made wholly independent of any consideration of pathology The reason for doing this was adequately explained in the previous chapter It is not that the pathology is unimportant it is not that we cannot learn from pathology but inasmuch as our direct and practical concern is with the entity at the clinical level it is important that any case made for blood lipids and their relationship with coronary heart disease be wholly independent of any of the pathological considerations In this way numerous questions criticisms and doubts can be resolved immediately since there is no dependence whatever on any pre-conceived

THE GENERAL PRINCIPLES INVOLVED IN TESTING FACTORS FOR RELATIONSHIP WITH CORONARY HEART DISEASE

In the evaluation of the significance of such factors as blood lipids and blood pressure in coronary heart disease certain highly important general principles are involved principles that can be utilized profitably in similar problems both with respect to other factors in coronary heart disease and with respect to factors related to any disease Such principles can be readily understood by combining their general features with a specific illustration of their practical clinical application utilizing in this case blood lipids in coronary heart disease

The suggestion that lipids of the blood might be associated with the development of coronary heart disease is a very old one which comes to our attention from a variety of types of evidence Listed previously were several of the areas of suggestion that the lipids of the blood might be important Among these are experimental induction of an arteriosclerotic lesion in animals by the feeding of cholesterol the finding that the lipids in the arteriosclerotic lesion are closely similar to the lipids of the blood the excessive incidence of coronary heart disease in families with xanthomatosis or with blood lipid disturbances and the excessive *incidence of coronary heart disease in diabetics at least in* the pre insulin era at which time many diabetics were frequently characterized by markedly elevated blood lipids These are all but clues falling short of provision of the direct answer concerning the role of blood lipids in the development of coronary *heart disease in the population at large It is precisely this group* with whom we are concerned since the overwhelming number of cases of coronary heart disease arise out of the population at large If the blood lipids were of consequence only for relatively special categories *such as the individuals with xanthomatosis* they would hardly be of much merit or significance with respect to the real problem of coronary heart disease which goes vastly beyond that of coronary disease in a highly special group of individuals such as xanthomatotic subjects Furthermore while the use of experimental animals such as the rabbit the chicken the dog the rat or the monkey for studies of arteriosclerosis is to be

such factors as age sex etc) but free of evidence of clinical coronary heart disease The presumption here is that while coronary heart disease is developing to a greater or lesser extent in those free of *overt* clinical disease on the average these individuals have a lesser degree of the disease and have been developing it at a slower rate than those of the same sex and age group who have already presented clinical signs and symptoms of coronary heart disease This presumption is actually closer to a definition for if *clinical* coronary disea e is the problem at hand it is obvious that those who manifest it have more of it than those who do not This represents one valid manner of approaching such a problem However there do exist certain fundamental objections to this approach alone First the measurements in those persons with clinically manifest coronary disease are being made *after* overt signs and symptoms are present Therefore it is impossible to know at what point in such a person s life any proven abnormality in blood lipids had appeared For utility in the direction of the ultimate objective of early interruption of sub-clinical coronary disease it is essential that the blood lipid factors under study be abnormal early in the *sub clinical phase* The study of persons with manifest coronary heart disease does not provide any way of knowing whether a factor (such as blood lipids) became abnormal shortly before clinical signs or had been abnormal many years before Indeed there is even a more dangerous possibility namely that the lipid abnormality appeared *after* the onset of clinical signs and symptoms either spontaneously or as a *result* of the clinical episode If this possibility were a reality the information would be u eless for the purpose we have in mind namely using the measurement of such factors to evaluate and rank people during the sub-clinical phase of coronary heart disease Even if the abnormality of the measurement appeared a very short time *before* clinical signs and symptoms the usefulness of the information would be extremely limited for purposes of identification of high risk candidates and for the institution of preventive measures Why then should one consider at all the measurement of some variable such as blood lipids in subjects with *overt* coronary disease in the effort to evaluate possible factors involved in its development? The

notions concerning the interrelationship of coronary arteriosclerosis with sub-clinical and clinical coronary heart disease

Thus the problem at hand is an evaluation of the blood lipid factor in the evolution of coronary heart disease as a clinical entity rather than as a pathological entity However our concern is mainly with the *sub clinical phase* of the clinical entity The type of study needed must bypass any pathology considerations and go directly to possible relationships between blood lipids and clinical development of coronary heart disease either in its sub clinical or manifest phases If blood lipids do represent a factor in the development of clinical coronary heart disease there must be *some* difference between the blood lipids of those humans with coronary heart disease and those humans without coronary heart disease Or if we regard coronary heart disease as a graded phenomenon rather than a yes or no phenomenon then there must be a progressive difference in the blood lipids as one passes from individuals with a low degree or rate of development of coronary heart disease to those with a higher degree or rate of development of this disease It is of no moment whether the blood lipids be higher with increasing degree of disease or lower with increasing degree of disease but there must be a *difference* in blood lipids in passing from those persons with less disease to those with more disease or those developing disease slowly in contrast with those developing disease rapidly

THE CHOICE OF SUBJECTS FOR STUDY

Evaluation of the relationships of blood lipids with coronary heart disease requires availability of some way to grade the degree *of disease or the rate of development in the subjects studied* But as was mentioned earlier no direct method exists to measure the degree or the rate of development of sub-clinical coronary disease which is precisely what we would most *like to* measure Two alternative choices suggest themselves

(a) Comparison of blood lipids in a group of subjects with documented manifest clinical coronary heart disease (in the form of angina pectoris or myocardial infarction) with the blood lipids in a group of subjects otherwise comparable (with respect to

ment of coronary disease could be identified by the blood lipid measurement at least 5 to 10 years before the transition to clinically overt disease. This type of evidence is precisely what is needed concerning sub-clinical coronary disease free of the objection that the clinical episode itself may conceivably have produced the abnormal blood lipid level.

ASSOCIATION, PREDICTION, AND CAUSE AND EFFECT

When a variable, e.g., blood lipid level, is measured in a disease entity such as coronary heart disease and in matched controls without overt heart disease and the mean level shows a difference between the two groups, whether higher or lower in the disease group than in the controls, it is possible to state that this variable is *associated* with the disease process. What the nature of that association is remains in any particular case to be demonstrated. No clear thinking scientist would ever claim that proof of association of a variable (such as blood lipids) with a disease (such as coronary disease) represents proof that the blood lipids are either *a* cause or *the* cause of the disease (such as coronary heart disease). But proof of association is the first step and indeed a vast and major step forward. This is an important issue since misunderstanding of this differentiation has led some investigators to *minimize* the significance of proven associations between a measurement *and* a *disease*. Such investigators are prone to state, "All this proves is association, but it doesn't prove cause and effect." And with such a statement they blithely pass off as of little consequence associations of major and practical clinical importance.

When an association has been proved between a measured variable and a disease, there are several possibilities that account for the association, among which are:

(a) The disease itself may cause the measured variable to be abnormal.

(b) Both the disease and the measured variable may be affected by an underlying metabolic or other defect which is itself the true cause.

(c) The abnormality in the measured variable may be the cause of the disease process.

answer is the highly practical one that alternatives to this are very costly of time and effort and hence delay progress in under standing The utilization of subjects with already established clinical signs and symptoms of coronary heart disease is of great value as an *introductory* procedure to this problem, for subjects are available in great numbers without the necessity of waiting for the clinical disease to develop in healthy persons Because of the limitations just described (i e not knowing whether any blood abnormality did or did not precede the clinical event) it is imperative to supplement studies of groups with overt disease with additional long term studies where the overt disease is per mitted to develop out of a population in apparent health at their initial study Thus in the case of coronary heart disease it is necessary to evaluate a variable of possible interest such as blood lipid level in a large sample of the population at a time when the persons involved are overtly well (which means that many are in various stages of *sub clinical* coronary heart disease) The size of the population sample requiring study depends upon (a) the frequency with which apparently healthy people develop clinically overt coronary disease and (b) the time period over which the subjects are observed A small sample observed over a long time period can usually yield the same information as a large sample observed for a short time period

The value of such a study should it reveal that those who later develop clinical coronary heart disease are either *higher* or *lower* in blood lipid level than the mean value for the population out of which they have grown is that it has been shown that the *blood lipid level is different for future coronary disease patients* from that for the population at large *at a time when such per sons are in the sub clinical phase of the disease* For example *if a follow up period averaging 1 year is utilized then it* would be known that the blood lipids are abnormal *at least* one year before the clinically overt disease is manifested If a follow up period *of 5 or 10 years is the average time period* for the cases of cor onary disease to grow out of the population then it would be known correspondingly that the abnormality in blood lipids was present 5 to 10 years before overt symptoms and signs Stated somewhat differently it would mean that sub clinical develop

ment of coronary disease could be identified by the blood lipid measurement at least 5 to 10 years before the transition to clinically overt disease This type of evidence is precisely what is needed concerning sub-clinical coronary disease free of the objection that the clinical episode itself may conceivably have produced the abnormal blood lipid level

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(a) The disease itself may cause the measured variable to be abnormal

(b) Both the disease and the measured variable may be affected by an underlying metabolic or other defect which is itself the true cause

(c) The abnormality in the measured variable may be the cause of the disease process

Ofttimes direct experimental choice among these three possibilities may be difficult or even impossible But this need in no way be discouraging for there are many indirect ways to solve the practical problem even though the direct proof may be lacking concerning the nature of the association

The three possibilities mentioned above deserve illustration and consideration with respect to the problem at hand namely coronary heart disease

The possibility that the disease itself is responsible for the abnormality in the measured variable in this case of blood lipids may be approached first If one had discovered the abnormality of the variable in patients who had had a myocardial infarction for example it is possible to believe that the metabolic alterations attendant upon occurrence of a myocardial infarction might have themselves been responsible for the abnormality in the measured factor (e g blood lipids) However this is precisely one of the reasons why one is not very satisfied with the discovery of an abnormal variable (such as blood lipids) in patients who have already manifested clinical myocardial infarction This is also the reason for the need to do *prospective* studies where the bio chemical measurements are made in individuals when they are in apparent health and where infarction or other clinical manifestations are then permitted to develop in a population of such individuals The possibility would still exist even in the study of the sub clinical disease to consider that the actual occurrence of the sub clinical disease developing might be the cause of the abnormal lipid measurements While patients developing sub clinical coronary disease show no evidence whatever of an illness that might be suspected to lead to metabolic aberrations the possibility cannot be ruled out that the disease itself is the cause of the abnormal lipid levels although it certainly would seem much less likely than would be the situation wherein patients are studied in the already clinically manifest phase of coronary disease Since the possibility cannot be ruled out one must consider what the implications of such a prospect are If for example identification of individuals with sub-clinical coronary disease is our objective and if the blood lipid abnormality were the *result* of the sub clinical disease this need not matter

in any way for our purposes The results would be just as valid for purposes of identification of individuals developing sub clinical coronary heart disease *whether* or *not* the disease caused the lipid abnormality However if our purposes are other than identification alone then it would make some difference whether the disease causes the lipid abnormality For example if one were interested in the possibility that correction of the lipid abnormality would have some effect upon amelioration of the disease the prospects would be dim if the *disease caused* the lipid abnormality The only conceivable way to determine this in the absence of direct information would be to make direct tests of the concept that decreasing the degree of the lipid abnormality in any way ameliorated the disease If such tests showed a positive result no further need would exist to raise the question of whether the disease caused the abnormality since the objective itself inhibition of the disease would have been realized In this sense it is entirely appropriate to allow our objective to determine our course of action rather than to wait until some indefinite future for the direct proof of whether or not the dis ease causes the abnormality or the abnormality is one factor which causes the disease

The second possibility is that the disease and the abnormality are both the result of some other feature be it a metabolic abnormality or some other property rather than that the lipid abnormality is the cause of the disease or the disease the cause of the lipid abnormality One could visualize for example that a metabolic dysfunction such as that in the liver might in some way alter blood lipids and by some wholly separate mechanism might provide an effect upon the cardiovascular system leading to coronary heart disease While such a possible mechanism is not immediately obvious it cannot be summarily dismissed In this case one might anticipate the possibility that alteration of the blood lipid factor (even though it has been proved to be asso ciated with the development of coronary heart disease) might not slow the rate of development of coronary disease This possi bility must be considered both with respect to prevention and therapy However two points are to be borne in mind in such a case First with respect to *prediction* of who is developing exces

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The possibility that the disease itself is responsible for the abnormality in the measured variable in this case of blood lipids may be approached first If one had discovered the abnormality of the variable in patients who had had a myocardial infarction for example it is possible to believe that the metabolic alterations attendant upon occurrence of a myocardial infarction might have themselves been responsible for the abnormality in the *measured factor (e g blood lipids) However this is precisely* one of the reasons why one is not very satisfied with the discovery of an abnormal variable (such as blood lipids) in patients who have already manifested clinical myocardial infarction This is also the reason for the need to do *prospective* studies where the bio chemical measurements are made in individuals when they are in apparent health and where infarction or other clinical manifestations are then permitted to develop in a population of *such individuals The possibility would still exist even in the* study of the sub-clinical disease to consider that the actual occurrence of the sub clinical disease developing might be the cause of the abnormal lipid measurements While patients developing sub clinical coronary disease show no evidence whatever of an illness that might be suspected to lead to metabolic aberrations the possibility cannot be ruled out that the disease itself is the cause of the abnormal lipid levels although it certainly would seem much less likely than would be the situation wherein patients are studied in the already clinically manifest phase of coronary disease Since the possibility cannot be ruled out one must consider what *the implications of such a prospect are* If for example identification of individuals with sub-clinical coronary disease is our objective and if the blood lipid abnormality were the *result* of the sub clinical disease this need not matter

disease some 30 years ago and as evidence accumulates it appears increasingly certain that his concept needs no appreciable modification

sive sub-clinical coronary heart disease the possibility of a third factor being the cause of both the lipid abnormality and the coronary heart disease *is of no moment whatever* For, all that is needed to achieve the requisite *predictive* information is the existence of a *relationship* between the blood lipids and the devel opment of sub clinical coronary heart disease whatever be the cause of either one of them Second the hypothesis of a third cause is simply an hypothesis based upon no facts Unless *some* facts develop *in its favor it is difficult to see why this more compli* cated hypothesis is chosen by some individuals rather than the simplest one *directly* relating the abnormality of the blood lipids with the development of coronary heart disease When one *chooses the simplest hypothesis this does not mean that one insists* on the correctness of it but rather that it *is* the simplest hypothe sis and therefore deserves careful and intense evaluation to deter mine its truth or falsity The actual practical evaluation of such an *hypothesis will of itself* provide *the best determination of cor* rectness Certainly this is an approach far superior to the entirely unwarranted assumption that the simplest hypothesis must be wrong Here again the practical issue is paramount If one *chooses to evaluate the simplest hypothesis that possibly the blood* lipids may be a *cause* of coronary heart disease and follows up the implications thereof namely whether lowering or altering the blood lipids will alter progression of coronary disease one may very *well* achieve the tremendous *clinical* result *which is* desired namely prevention or minimization of coronary heart disease The practical test itself will have laid to rest much of the need for consideration of possibilities of a more complicated relationship *Until and unless this* extremely *important possibil* ity has been shown to be incorrect by direct clinical test thereof it remains the most attractive hypothesis deserving of study For in the case of blood lipids and coronary disease one is led to this simplest *hypothesis not only by a strong set of data namely asso* ciation between the blood lipids and sub-clinical coronary heart disease but also by massive indirect evidence which suggests that the relationship is truly a causal one Anitschkow[4] suggested *the causal relationship between blood lipids and coronary heart*

exist as such circulating in the blood stream Thus even such a term as free cholesterol or esterified cholesterol is misleading since it tends to *indicate* or to suggest that these are two separate entities circulating *as such* in the blood This is not the case There can be demonstrated no evidence for any significant quantity of cholesterol circulating in the blood as such or of phospholipids circulating in the blood as such or of triglyceride circulating in the blood as such or of fatty acids circulating in the blood as such Instead all of these chemical constituents which comprise the lipids of blood are substructural units or building blocks for a series of very large molecules that do exist as such in the blood and which have been designated as *lipoproteins* The designation lipoproteins simply implies the presence of structural entities in the blood comprised in part of lipid and in part of protein The designation itself does *not imply* any specific protein or any particular lipid Therefore whether cholesterol cholesterol and phospholipid or cholesterol phospholipid neutral fat and fatty acid are all present in a particular lipoprotein is not the feature required to allow this definition or designation If any one of the lipid entities is associated with protein to form a macromolecular structure such a structure would be referred to as a lipoprotein The lipoproteins are molecules of very large size even the *smallest* lipoprotein being larger in size than a serum globulin molecule The lipoproteins are *the* transport vehicles for the lipids in blood Many investigators have commented on nature s need to solubilize the lipids in blood through the attachment of the various lipids to protein Whatever the merits of this type of reasoning it can hardly add anything to the statement that lipids are transported essentially completely in the form of a series of lipoproteins The lipoproteins of blood represent not a single or a few specie (s) but rather a whole range of molecular entities from sizes approximating that of gamma globulin *to tremendous sizes* such as those familiar from dark field microscopy as the chylomicrons A compound such as cholesterol finds itself as a constituent of every single class of lipoproteins that has been analyzed Therefore we have immediately before us the possibility of the various lipoproteins differ in concentration from person to person which they do

Chapter III

THE BLOOD LIPID FACTOR IN CORONARY HEART DISEASE

A PREREQUISITE to evaluation of the blood lipid factor in coronary heart disease is a concept of our present day knowledge of the nature of the circulating blood lipids. Two major modalities of characterization have been applied to the blood lipids, the first being chemical and the second being largely physical in nature. Historically the chemical characterization preceded the physical characterization, primarily the result of the earlier availability of chemical techniques for analyses. There can, of course, exist no *real* conflict between such modalities of analysis, nor can there be any inconsistency in the results derived therefrom, providing both types of analyses are correct. There exist, however, many good reasons to consider that the more modern physical techniques for analysis of the blood lipids may be of the greater value. For the physical techniques describe the blood lipids in a state resembling closely that in which they exist in the blood. Second, they provide a more intimate characterization and delineation of the various blood lipids of potential interest in the problem of coronary heart disease. The detailed basis for these statements will become apparent in later discussions.

Chemically, the lipids of the blood are comprised largely by cholesterol, some of it free and some of it esterified with various fatty acids, triglyceride or neutral fat, phospholipids, free fatty acids, and possibly by several other constituents at very low abundance. The first three are certainly the major constituents on the basis of abundance. The results of modern physico-chemical techniques applied to the problem of the blood lipids show clearly that the chemical entities described above do not

rates even though very small molecules (such as glucose) do not The second property of lipoproteins that makes them especially adaptable to ultracentrifugal analysis is the fact that they possess a physical density (grams/milliliter) that is considerably different from the density of the much more abundant *proteins* of blood Whereas the density of the proteins of blood is approximately 1 3 grams per milliliter the density of the most dense lipoproteins of blood is only 1 15 and the density of other lipoproteins range downward from this value to values even below 1 gram per milliliter This means that if a solution is prepared from serum by the addition of sodium chloride or some other salt or sugar which thereby places the solution density between the density of the lipoproteins and that of the proteins it is possible to effect a neat separation of the proteins and lipoproteins The lipoproteins then *float* in the ultracentrifuge while the proteins *sediment* This is the first step in lipoprotein analysis of serum Once the lipoproteins have been separated from the proteins by this method they are available for the step known as the analytical step which utilizes a larger ultracentrifuge equipped with an optical system for determining the kinds of lipoproteins that are present and the concentrations of each type present in a serum sample It is customary in ultracentrifuge practise to refer to the speed to which any particle migrates under the effect of an intense gravitational field as its sedimentation rate or *migration* rate in S units The S stands for Svedberg and is so named in honor of The Svedberg who invented and pioneered the ultracentrifuge Thus if one were speaking about serum albumin molecules which migrate in an ultracentrifuge under standardized conditions with 4 arbitrary units of speed the albumin molecules would be referred to as molecules of the 4S or 4 Svedberg class The *proteins* which are more dense in general than the solutions in which they are migrating sediment outward in the centrifugal field or in the direction of the centrifugal field The units of migration are chosen to be positive in this direction so albumin would have a migration rate of *plus* 4 units of speed in Svedberg units However under the usual circumstances of lipoprotein analysis the lipoproteins are made to undergo flotation *toward* the center of rotation rather than

that a specified amount of cholesterol in the blood can mean very different things from one person to another The same considerations would apply to phospholipids or to triglyceride a specified amount of *either of these substances meaning possibly* very different things in different people This can be restated that a specified chemical constituent (such as cholesterol) in one person may be primarily in one type or in a few types of lipoprotein whereas in another person that same chemical compound might be distributed *primarily in other types of lipoprotein* The intimate characterization of the lipoproteins in the blood and their measurement is at present most effectively and easily achieved by the physical technique of ultracentrifugation There is no other method which provides the detail concerning the distribution of types of lipoproteins in the blood and the measurement of the various classes that is even remotely comparable with the quality of data obtainable via the ultracentrifugal technique That this technique will in the future be the best way of analyzing the lipoprotein distributions in blood is of course not foreseeable Should any simpler more effective or more critical technique be evolved it would certainly be of great value to utilize such a newer technique for the analysis of the blood lipoproteins although at present no such technique is in the offing One might ask whether other techniques are available which for practical clinical purposes might serve adequately even though for research purposes the ultracentrifugal technique is a necessity The answer is that some of the highly practical *clinical* questions (which will be dealt with later in this book) require the ultracentrifugal analysis of the distribution of serum lipoproteins for most effective identification of the type of disorder involved and for the handling of those disorders in a medical management sense There are two properties of the lipoproteins of human blood which make the ultracentrifuge especially useful in their analysis The first property of the lipoproteins is their very large size The ultracentrifuge is an instrument which is in principle the same as an ordinary centrifuge and hence particle size is of major consequence With the powerful centrifugal fields available in the ultracentrifuge the lipoproteins in the blood are of large enough size to migrate at reasonable

flotation rate in S units and that their concentrations can be measured in the usual clinical terms of milligrams per hundred milliliters directly from the ultracentrifugal analyses There is one caution however that is important to stress In the earliest centrifuge work lipoproteins were studied in a relatively dilute solution and their values were reported *directly* in terms of migration rates in S units However for certain purposes of precision and accuracy it became convenient to study the lipoproteins ultracentrifugally in more concentrated solutions Under these conditions lipoproteins tend to slow themselves down in migration rate because of their being in high concentration As a consequence all migration rates must be corrected in a standard manner before reporting of results This correction can be very precisely applied and should be applied There is no question of error involved in the use of concentrated solutions provided the appropriate corrections are applied When this *correction* is applied the lipoproteins are reported in terms of *Standard* S_f *units or* s_f units The word standard or the superscript zero applied to S_f means that the worker has applied all the corrections necessary for proper analysis of ultracentrifuge diagrams Certain workers in the field have not fully appreciated the significance of the necessity to report ultracentrifuge results in the standard flotation rate or s_f units and have used concentrated solutions for ultracentrifugal analyses without applying the corrections They have reported their work directly in S units Such work is neither comparable to the early work in dilute solution[13] nor is it comparable to the correct method of ultracentrifugal analysis employing standard S units Therefore the reader is urgently cautioned to view with skepticism any report of ultracentrifugal analyses of lipoproteins in disease states or in health where concentrated solutions have been utilized and where the results are reported in uncorrected S units instead of the standard S units in which they should be reported A case in point where erroneous clinical conclusions were reached because of failure to utilize standard flotation rates is in the work of certain laboratories reported in the so-called Cooperative Study of Lipoproteins and Atherosclerosis[14]

The lipoproteins of human blood are divided into two broad major groups the group of largest abundance and of primary

outward in the direction of the centrifugal force In other words since the lipoproteins are migrating in a solution more dense than themselves, they migrate inward against the direction of centrifugal field In order to avoid the cumbersome use of negative units for such flotation a unit was introduced some ten years ago known as the *Svedberg of flotation or Sf unit*[11] This means precisely the same in terms of units of speed as for the proteins except that materials are floating instead of sedimenting Thus if a lipoprotein floats as fast as albumin sediments the lipoprotein is called a molecule of the 4Sf class to correspond to the nomenclature of 4S for the albumin molecule The description of lipoproteins in terms of flotation rate in Sf units is more than just a physical measurement since it proves convenient as an actual naming system for the various lipoproteins Had it turned out that nature were extremely simple and there were only a few lipoprotein species present in human blood they might have been *named by such terms lipoprotein one two and three or lipoprotein* A B and C However the studies of human blood have shown that there exists an entire host of lipoproteins ranging in size from the smallest which are approximately 200 000 in molecular weight up to the largest which are millions of millions in molecular weight with a great number of intermediary species being known to exist There just wouldn t be enough letters in the alphabet to name them by arbitrary names Furthermore naming of the lipoproteins by the physical measurement of the number of Svedbergs of flotation of migration rate proves to be very useful for the name means something in terms of a physical constant that can be reproduced under standard conditions by workers anywhere in the world with ultracentrifugal equipment In all the subsequent discussions of the relationships of lipoproteins with coronary heart disease lipoproteins will be named in terms of their migration rate in the ultracentrifuge under a set of arbitrarily defined standard conditions in Sf units The precise technical details of ultracentrifugation have been described in extenso elsewhere[12] *It is neither the purpose of this discussion* nor this book to present such technical issues in detail For our present purposes it is sufficient to note that a large number of lipoproteins exist in human serum that they are named by their

teins between any two of these dividing points The sum of con centrations of all the lipoproteins between flotation rates of s_f0 and s_f12 is referred to as the concentration of the s_f0 12 lipopro tein class Correspondingly the sum of concentration of all the lipoproteins floating between the rates of s_f12 and s_f20 is referred to as the concentration of the s_f12 20 lipoprotein class Similar procedures are used to determine the s_f20 100 and s_f100-400 lipo protein classes Most lipoprotein analyses are reported in these general bands The question may be raised as to whether there might not be some better banding or some sub banding that would be of importance Such a possibility can never be ruled out but it can be stated that if in the future a different banding should be proved to be of greater value an old ultracentrifugal run can be re evaluated in terms of such new banding At the moment there appears to be little advantage with respect to the study of a disease such as coronary heart disease of any banding beyond that which has already been described Indeed for certain purposes the three classes s_f12 20 s_f20 100 and s_f100-400 lipoproteins are added to gether and reported as the s_f12-400 lipoprotein class This type of procedure is one of general applicability Thus if the concen trations of s_f20 100 and s_f100-400 lipoproteins are added the sum of these two concentrations can be referred to as the concentration of the s_f20-400 lipoprotein class

It is now possible to turn attention to the problem of whether or not any of the lipoproteins of human blood are associated in some way with coronary heart disease The ultimate objective sought might be restated here namely a measurement which would be related in a *predictive* sense to the rate of development or of the degree of development of sub-clinical coronary heart disease If human blood lipoproteins are found to be associated with coronary heart disease the first question that must be asked is *Which* lipoproteins are involved the s_f0 12 class the s_f12 20 class the s_f20 100 class or the s_f100-400 class or some combination of these classes? The next question to be answered is If all classes or several classes of lipoproteins are involved does the measurement of each class provide *independent* information? It is of course possible that one class of lipoproteins may be simply a rider being abnormal simply because the level of this class of

interest with respect to coronary heart disease being that known as the low density lipoproteins Such lipoproteins are all characterized by densities of 1 05 gms/milliliter or less There are in addition, three groups of lipoproteins which are referred to as high density lipoproteins all of densities 1 05 gms/milliliter or greater The high density lipoproteins will be referred to in a subsequent chapter under the subject of various chemical analyses in connection with prediction tests for coronary disease (Chapter XV) and will not be dealt with further at this point The low density lipoproteins under standard conditions or in Standard S_f units migrate with rates of 0 units up to some 40 000 units of speed In the vast majority of human cases the bulk of these *lipoproteins are contained within the range of speeds from 0 to 400* units This band is also incidentally the most readily studied by ultracentrifugal procedures Even within the region of S_f0 to S_f400 there exists a very large number of lipoprotein species One cannot be sure at this time of the exact number of species that is present If measurements were to be made of lipoproteins in relationship to coronary heart disease the analysis of concentration of each and every lipoprotein class from S_f0 to S_f100 would be an almost insurmountable task However, there are alternatives to measurement of each and every lipoprotein within this region from S_f0 to S_f100 alternatives which have been shown to be highly productive One such alternative is to divide the region from S_f0 to S_f400 into several bands The actual choice of limits of bands is somewhat arbitrary although there appear to be some regions of logical sub division Such regions were chosen through large experience with ultracentrifugal analyses which revealed that points such as S_f12 S_f20 and S_f100 are what might be called natural dividing points Many humans show a minimum in their lipoprotein concentrations in these particular regions As a result of using such dividing points lipoproteins are characterized as those which float between the rates of S_f0 and S_f12 those which float between the rate of S_f12 and S_f20 those which float between the range of S_f20 and S_f100 and those which float with rates between S_f100 and S_f400 A convenient practical procedure that has been utilized in over 100 000 routine ultracentrifuge analyses of human blood is to measure the sum of the concentrations of all lipopro

ing such investigations In such a study one is desirous of minimizing any disturbing factors extraneous to the factor of the existence of clinical coronary heart disease itself Thus to contrast the serum lipoprotein levels in patients with clinically established coronary heart disease with persons in overt health (those without clinical manifestations of coronary heart disease) one would not like to have the patients with clinical coronary heart disease in a metabolic state unusual for them For example one would prefer to have patients who are on the same diet which has characterized them during the period of life before their clinical manifestation of heart disease The possibility had existed and has now been abundantly confirmed that dietary change can of itself profoundly alter serum lipoprotein levels One would prefer that the patients be at precisely the same weight that had habitually characterized them before their episode of clinical coronary heart disease One would prefer that they be taking no medications that they were not taking before their episode of clinical coronary heart disease Quite obviously the various clinical sources of material available for this type of study do not allow for attainment of such ideal clinical cases For many many years numerous physicians have had definite ideas concerning diet weight control and certain medications in relation to coronary heart disease wholly apart from blood lipid considerations Hence patients who present with clinical coronary heart disease have necessarily received some advice and management which may alter their metabolic status Nevertheless one can exclude cases where more than a certain amount of weight has been lost since the clinical episode and if such exclusions are made before the lipoprotein analyses are available there is very little possibility of biassing the material in this way Furthermore in the very acute phase of an episode such as myocardial infarction there is the possibility of shock and its attendant metabolic alterations which one would also want to avoid For this reason the study of patients with clinically established coronary heart disease has been limited to those who were at least six weeks beyond the occurrence of an acute episode of myocardial infarction The acute phase has been studied in addition but this was not part of the original program of evaluation The question of matched con

lipoproteins may be highly correlated with the level of some other lipoprotein class that is directly involved in coronary heart disease A third major question that would arise is At what stage in the evolution of coronary heart disease does any association between lipoproteins and the disease first manifest itself? In the general discussion of possible factors associated with coronary heart disease it was pointed out that if a variable becomes abnormal *after* the clinical event is manifest but is not abnormal or unusual during the sub clinical stage it would not be of especial interest for the purposes desired Therefore it is urgent to know how early in the evolution of the sub clinical phase of coronary heart disease any disturbance of lipoprotein levels does manifest itself

For reasons of convenience and availability of material the earliest studies made concerning the possible association of lipo proteins with coronary heart disease were made on patients with established clinical coronary heart disease The objections to the use of such clinical material as a final group were reviewed in detail in Chapter II, where it was demonstrated however that such material is an excellent starting point in this problem As was also pointed out earlier the alternative to the use of such material is to study a very large number of apparently healthy people and then to watch the evolution of coronary heart disease *in this group Such studies would allow not only for proof of* association of lipoproteins with sub clinical coronary heart dis ease but also a determination of how early in the sub clinical phase of the disease any abnormality of lipoproteins is present Both types of studies have by now been completed with highly conclusive results and the results of both types of studies will be presented below

THE STUDY OF LIPOPROTEINS IN PATIENTS WITH CLINICALLY MANIFEST CORONARY HEART DISEASE

While the study of patients with clinically established coro nary heart disease leaves undetermined the issue of whether the clinical event might have possibly caused any abnormality dis covered in serum lipoproteins the great availability of clinical material *without a long delay period* such as a prospective fol lowup study entails made this the procedure of choice for start

nent is that the control subjects be closely comparable to the clinically diseased subjects except for the one fact that the control subjects do not show clinically manifest coronary heart disease. It is of no moment whatever to obtain a group of subjects as controls who are free of any possible tinge of sub-clinical coronary heart disease.

Studies have been made of all the four major low-density lipoprotein classes, S_f 0-12, S_f 12-20, S_f 20-100, and S_f 100-400, in several age categories of males with and without clinical coronary heart disease in the form of documented myocardial infarction and in several age categories of females with and without clinical coronary heart disease. The mean values for each of these lipoprotein classes in the subjects with clinical coronary heart disease and their matched controls are presented in Table I. It is evident from statistical analyses of these data for the sub segments of the entire series of patients where there are adequate numbers of cases or for the entire series of cases and their age and sex matched controls that the following is true:

(1) The S_f 0-12 lipoproteins are significantly and appreciably higher in the clinical coronary heart disease cases than in their matched controls.

(2) The S_f 12-20 lipoproteins are significantly and appreciably higher in the coronary disease cases than in their matched controls.

(3) The S_f 20-100 lipoproteins are significantly and appreciably higher in the coronary disease cases than in their matched controls.

(4) The S_f 100-400 lipoproteins are significantly and appreciably higher in the coronary disease cases than in their matched controls.

The first large step forward can be taken, namely, to make the statement that the low-density serum lipoproteins are distinctly different, on the average, in patients with clinical coronary heart disease from those in their matched controls. It can be stated further that elevated levels of several serum lipoprotein classes are in some way associated with clinical coronary heart disease. Next must come the issue of whether *independent* information is provided by the measurement of *each* of these four lipoprotein classes

trol subjects arises Certain aspects of the choice of control subjects should be obvious among these are such aspects as matching the cases of clinical coronary heart disease by sex age and by general source of origin of the subjects Since ideally the study to be described subsequently is the one of choice namely where the coronary disease group arises de novo out of a previously studied large population sample it is desirable in this study which compares persons with and without overt clinical coronary heart disease that as nearly as possible the control subjects be representative of the population segment out of which the clinical coronary disease cases had arisen For example it would be extremely poor matching if one were to use indigent patients with coronary heart disease as the disease subjects and a well to do population sample as the control subjects or vice versa This is not an academic matter at all since the problem of selection of sources of clinical material is a very serious one often inadequately appreciated by clinical investigators

One source of confusion has especially plagued the minds of many who have considered the evidence relating blood lipid findings with coronary heart disease This is the question of whether or not the control subjects are free of coronary atherosclerosis First of all it should be stated that this entire question of the difference in blood lipids between subjects with clinical coronary heart disease and control subjects is being developed wholly without any reference to atherosclerosis Hence there is simply no need whatever to ask the question of whether or not the control subjects are free of coronary atherosclerosis Second even if we were to ask the question of whether there does exist sub-clinically some degree of coronary heart disease going on in those who have not yet manifested clinical symptoms the fact that the answer is yes is wholly immaterial to the issues at hand At this point we are simply asking the question Is there a difference in lipoprotein levels of the various lipoprotein classes between those individuals who have demonstrated documented clinical coronary heart disease and those who have *not* demonstrated clinical coronary heart disease? There is no inference intent to infer or effort to prove that subjects chosen as controls are free of sub-clinical coronary heart disease All that is perti

In essence the question to decide is whether S_f12 20 lipoproteins are *intrinsically* elevated in clinical coronary heart disease or whether they are elevated simply as a reflection of the elevation in S_f0 12 lipoproteins which characterizes clinical coronary heart disease. Perhaps another way to express this concept more clearly would be to ask the question: If *all other things* were equal concerning the cases of clinical coronary heart disease and the matched controls, would the S_f0 12 lipoproteins still be elevated in the coronary disease cases? Similar questions could be asked for the observed elevation in level of the S_f12 20 lipoproteins, the S_f20 100 lipoproteins, and the S_f100 400 lipoproteins respectively. This approach can be made more simply if at first the total group of lipoproteins from S_f0 to S_f400 is subdivided into two major classes, S_f0 12 and S_f12-400 bands, instead of into four groups. Then if the cases of documented myocardial infarction are matched with random control cases *at the same* S_f0 12 lipoprotein levels, is it true that the S_f12 400 lipoproteins are *still* elevated in the coronary disease cases relative to those in the matched controls? The direct tests of this issue are presented in Table II. The results there provide excellent evidence that the cases of myocardial infarction matched with the control cases upon S_f0 12 lipoprotein level do

TABLE II

DEMONSTRATION OF THE INDEPENDENT ELEVATION OF S_f12 400 LIPOPROTEIN LEVELS IN MYOCARDIAL INFARCTION CASES IN COMPARISON WITH MATCHED CONTROLS

(Myocardial infarction cases matched with random controls upon age, sex and upon S_f0 12 lipoprotein levels)

Group	Number of Cases	S_f0 12 Lipoprotein Level (mg/100ml)	S_f12-400 Lipoprotein Level (mg/100ml)
40 49 year old male Myocardial Infarction Survivor	113	4[illegible]0.4	3[illegible]1.6
40 49 year old Matched Controls	113	[illegible]	2[illegible]
Difference (Myocardial Infarctions – Controls)			+ 6[illegible] (p<<0.001)

The slight difference in S_f0 12 lipoprotein level between the infarction cases and the controls indicates how well the two groups were matched upon this variable.

TABLE I

SERUM LIPOPROTEIN LEVELS IN PERSONS WITH AND WITHOUT OVERT CLINICAL CORONARY HEART DISEASE

(Myocardial Infarction as Criterion)*

MALES	Mean Age (years)	Number of Cases	Mean S_f 0 12 Level (mg/100ml)	Mean S_f 12 20 Level (mg/100ml)	Mean S_f 20 100 Level (mg/100ml)	Mean S_f 100 400 Level (mg/100ml)
30 39 year age group						
Myocardial Infarction	31 8	11	485 0	104 3	152 1	72 3
Matched Controls	34 8	934	356 2	51 5	92 ,	52 0
40 49 year age group						
Myocardial Infarction	44 5	113	420 4	88 7	134 3	98 7
Matched Controls	44 5	339	382 9	57 0	108 5	67 2
50 59 year age group						
Myocardial Infarction	54 0	210	413 4	83 3	124 3	77 3
Matched Controls	54 0	153	385 3	56 2	106 0	60 0
60 69 year age group						
Myocardial Infarction	63 9	144	40/ 7	82 2	121 2	61 7
Matched Controls	63 9	35	365 5	52 5	92 0	43 5
FEMALES						
35 69 year age group						
Myocardial Infarction	57 2	59	426 8	110 8	116 4	99 2
Matched Controls	r7 2	110	367 0	r4 5	87 8	26 0

*All myocardial infarction cases represent survivors eight weeks or more beyond the acute episode

In essence the question to decide is whether s_f12-20 lipoproteins are *intrinsically* elevated in clinical coronary heart disease or whether they are elevated simply as a reflection of the elevation in s_f0-12 lipoproteins which characterizes clinical coronary heart disease. Perhaps another way to express this concept more clearly would be to ask the question: If *all other things* were equal concerning the cases of clinical coronary heart disease and the matched controls would the s_f0-12 lipoproteins still be elevated in the coronary disease cases? Similar questions could be asked for the observed elevation in level of the s_f12-20 lipoproteins, the s_f20-100 lipoproteins and the s_f100-400 lipoproteins respectively. This approach can be made more simply if at first the total group of lipoproteins from s_f0 to s_f100 is subdivided into two major classes, s_f0-12 and s_f12-400 bands instead of into four groups. Then if the cases of documented myocardial infarction are matched with random control cases *at the same* s_f0-12 lipoprotein levels, is it true that the s_f12-400 lipoproteins are *still* elevated in the coronary disease cases relative to those in the matched controls? The direct tests of this issue are presented in Table II. The results there provide excellent evidence that the cases of myocardial infarction matched with the control cases upon s_f0-12 lipoprotein level do

TABLE II

DEMONSTRATION OF THE INDEPENDENT ELEVATION OF S_f12-400 LIPOPROTEIN LEVELS IN MYOCARDIAL INFARCTION CASES IN COMPARISON WITH MATCHED CONTROLS

(My[illegible]ard[illegible]l [illegible]nfarct[illegible]on cases ma[illegible]che[illegible] [illegible]ith random controls upon age, s[illegible]x a[illegible]d u[illegible]on S_f0-12 lipoprote[illegible]n lev[illegible]ls)

C[illegible]o[illegible]p	Number of C[illegible]ses	S_f0-1[illegible] Lipoprotein Level ([illegible]g/100m[illegible])	S_f12-400 Lipoprotein Level (mg/100ml)
40-4[illegible] year old male Myocardial Infarction Surv[illegible]vo[illegible]	113	4[illegible]0.4	321.6
40-49 year old Matched Co[illegible]t[illegible]ols	113	4[illegible]2.2	2[illegible]4
	Difference (My[illegible]car[illegible]al Infarctions – Controls)		+ 6[illegible].2 (p<<0.001)

Th[illegible]e [illegible]light d[illegible]fference in S_f0-1[illegible] [illegible]ip[illegible]protein level b[illegible]e[illegible]een the infarction cases and the [illegible]o[illegible]t[illegible]ol[illegible] [illegible]d rates [illegible] [illegible]ell the t[illegible]o groups [illegible]e[illegible]e matched upon th[illegible]s variable

show a higher mean S_f12 400 lipoprotein level than do the controls Therefore evidence is at hand of the independent association between coronary heart disease and the S_f12-400 lipoprotein levels Stated otherwise while we get evidence from the measurement of S_f0 12 lipoprotein levels concerning coronary heart disease we derive *additional* and truly independent information from the measurement of the S_f12 400 lipoprotein levels

Similarly, the problem can be approached the other way around If the documented cases of myocardial infarction are matched with random control cases at the same S_f12-400 lipoprotein level, is it true that the S_f0 12 lipoprotein levels are still elevated in the coronary disease cases as compared with the matched controls? A direct test of this point was made the results of which are presented in Table III Those results indicate clearly that even when the myocardial infarction cases are matched with the control cases *at the same values of the S_f12-400 lipoproteins* the myocardial infarction cases still show a significantly and appreciably higher level of S_f0 12 lipoproteins than do the matched controls Therefore this provides direct evidence for the independent association of the S_f0 12 lipoproteins with coronary heart disease Thus while we get evidence from the measurement of the S_f12 400 lipoprotein levels concerning coronary heart disease

TABLE III

DEMONSTRATION OF THE INDEPENDENT ELEVATION OF S_f0 12 LIPOPROTEIN LEVELS IN MYOCARDIAL INFARCTION CASES IN COMPARISON WITH MATCHED CONTROLS

(Myocardial infarction cases matched with random controls upon age sex and upon S_f12-400 lipoprotein levels)

Group	*Number of Cases*	*S_f12 400 Lipoprotein Level (mg/100ml)*	*S_f0 12 Lipoprotein Level (mg/100ml)*
40 49 year old male Myocardial Infarction Survivors	113	321 7	420 4
40 49 year old Matched Controls	113	322 8*	381 9
Difference (Myocardial Infarctions Controls)			+ 38.5 (p << 0 001)

The slight difference in S_f12 400 lipoprotein level between the infarction cases and the controls indicates how well the two groups were matched upon this variable

we derive *additional* and independent information from the measurement of the S_f 0 12 lipoprotein levels

Looking ahead to some of the applications of these findings it becomes apparent why such information is crucial If two independent groups of lipoproteins determine a person s status with respect to coronary heart disease it is clear that the measurement of only *one* of these groups cannot possibly provide a complete picture of that person s status A person might for example be quite satisfactory in terms of his level of S_f 0 12 lipoproteins and hence his outlook with respect to coronary disease be considered good on this basis but on the other hand with an enormously elevated level of S_f 12-400 lipoproteins the outlook would be changed to a poor one in spite of the favorable level of the S_f 0 12 lipoproteins

In an entirely analogous manner each of the subcomponents of the S_f 12-400 group of lipoproteins namely the S_f 12 20 S_f 20 100 and S_f 100-400 lipoproteins can be tested for independent association with clinical coronary heart disease This has been done successively for each of these lipoprotein classes[1] It can be stated that S_f 12 20 lipoproteins S_f 20 100 lipoproteins and S_f 100-400 lipoproteins respectively are all *independently* associated with clinical coronary heart disease

In summary the study of *established* clinical coronary heart disease (utilizing documented myocardial infarction cases) is that low-density lipoproteins of the blood at least of these four classes the S_f 0 12 12 20 20 100 *and a 100-400* classes are significantly elevated in clinical coronary heart disease and that each class of lipoproteins provides information independent of that provided by all the others *Therefore* the best evaluation of a person s status would be available if the measurement of each of the four classes were made *In the* general discussion (Chapter II) it was pointed out however that there exist certain potential pitfalls in the application for predictive purposes in the sub clinical phase of coronary heart disease of information derived from the study of after the fact cases of clinical coronary heart disease Among such potential pitfalls is the possibility that a clinical episode of coronary heart disease itself is the cause of the lipoprotein elevation The only way to evaluate this possibility

is to show whether the association between lipoprotein levels and coronary heart disease holds *during the sub clinical phase,* well in advance of the clinical episode This involves the study of lipoprotein levels in a reasonable sample of the population at large with follow up observation for the development of de novo clinical coronary heart disease

THE PROSPECTIVE STUDY OF THE RELATIONSHIP BETWEEN SERUM LIPOPROTEINS AND CORONARY HEART DISEASE IN ITS SUB CLINICAL STATE

The major potential value of what association exists between lipoproteins and coronary heart disease lies in the extent of such association during the sub clinical phase Any association demonstrated for the sub clinical phase provides immediately information of potential value in the advance prediction of clinical coronary heart disease and of potential value in the guidance of a program for prevention of clinical coronary heart disease It was recognized early in the study of this problem that development of the information concerning the nature of the association of the sub clinical coronary heart disease with serum lipoproteins was absolutely essential The establishment of the relationship of the serum lipoproteins with *clinical* coronary heart disease was an early step possible because of the ready availability of material Those studies did provide a great deal of information of use while the results of the prospective study in the sub clinical phase were awaited The essence of a study designed to determine whether the association that has been proven between serum lipoproteins and clinical coronary heart disease also holds in the sub clinical phase centers about follow up observations A large population sample of individuals in overt health that is free of any evidence of clinical coronary heart disease is studied with respect to lipoprotein levels Then for a period of one or more years such individuals are observed without any effort being made to alter their lipoprotein levels and indeed without them being aware of the findings of the lipoprotein analysis If the sample of the population studied is sufficiently large then over a period of one to three years there is expected a reason

able incidence of development of manifestations of clinical coronary heart disease in the form for example of angina pectoris myocardial infarction or death due to coronary heart disease Since angina pectoris is a subjective diagnosis this is the least safe to use as a clinical manifestation of the development of coronary heart disease Hence in the considerations of an association between the sub-clinical phase of coronary disease and lipoproteins the development of angina pectoris was not used as a primary criterion However documented myocardial infarction coronary thrombosis with death and sudden death due to coronary heart disease were used as acceptable events of a clinical type to identify those individuals who passed from the subclinical phase of coronary heart disease to the clinical phase If the lipoprotein association with coronary heart disease which was proven above with respect to the clinical phase also holds in the sub-clinical phase it would be expected that the mean level of the various classes of lipoproteins in those individuals in the population sample who develop clinical coronary heart disease will be the same as the mean level found in the cases of established clinical coronary heart disease This would be so unless the clinical coronary heart disease has of itself altered the lipoprotein levels or that some factor attendant upon clinical coronary heart disease such as alteration in diet or medication has altered the lipoprotein levels If the lipoprotein elevation is an abnormality present before the *clinical event* and is unaltered by the clinical event itself then it would be expected that the lipoprotein level determined in a group of people before they have a myocardial infarction should be the same as in such groups of people studied after the infarction

The requisite large scale follow up study has now been completed[16 17] Several sources of men in clinical health were utilized to provide lipoprotein samples before the follow up observation period These sources included

(1) Persons involved in the Framingham United States Public Health Service Heart Project

(2) Employees of the Eastman Kodak Corporation

(3) Employees of United Air Lines

(4) Employees of the Los Angeles Civil Service Commission

(5) Employees of Pan American Airlines

(6) Employees of the University of California Radiation Laboratory

In all there were 4 088 subjects under study During a one to three year follow up period the period being variable for the various sources there occurred 26 cases of documented myocardial infarction coronary thrombosis or coronary heart disease with death in individuals who had been previously classified at the time of entry into the study as being in clinical health Since being in clinical health means only that overt manifestations of coronary heart disease are absent this is of course tantamount to saying that such individuals were *in various stages of the development of sub clinical coronary heart disease,* since this is the real meaning of sub clinical coronary heart disease In Table IV are listed the cases of proven documented clinical coronary heart disease which have evolved out of the population sample under follow up together with their lipoprotein values for the various classes Also in Table IV are given the mean values for the matched population sample itself out of which the cases have arisen matched by age with the cases of documented de novo *coronary heart disease (according to the above listed criteria)* These data show clearly that the persons who later develop clinical coronary heart disease are those who were previously shown to have elevated lipoproteins of the four low density lipoprotein classes s_f0 12 s_f12 20 s_f20 100 and s_f100 400 Furthermore the *extent of lipoprotein elevation that had characterized the de* novo cases one to three years before is closely similar to that found previously for established cases of coronary heart disease described above These data establish conclusively that the lipoprotein associations previously proven for clinical coronary heart disease *also hold for the sub clinical phase at least* one to three years before the clinical phase This of course implies that lipoprotein measurement *must* have predictive value in selecting out the likely candidates for the future development of clinical coronary heart disease The exact manner in which such data are used for such predictive purposes will be treated in Chapter V

However at the present time it is important to point out that the data derived from the prospective follow up study show clearly that none of the concepts concerning lipoproteins and coronary heart disease derived from the study of the established clinical entity were in any way incorrect or misleading Indeed the agreement between the study of established coronary heart disease and de novo coronary heart disease could hardly have been better

There had previously existed much indirect evidence which would have suggested that the abnormality in blood lipids

TABLE IX (a)

LIPOPROTEIN LEVELS IN 26 MEN (DETERMINED WHILE THEY WERE CLINICALLY HEALTHY) WHO SUBSEQUENTLY DEVELOPED DOCUMENTED CLINICAL CORONARY HEART DISEASE

(1 to 3 year follow up period)

Case	Age at Study	S_f 0 12 (mg/100ml)	S_f 12 20 (mg/100ml)	S_f 20 100 (mg/100ml)	S_f 100-400 (mg/100ml)
1	34	576	85	155	139
2	55	719	139	271	131
3	[illegible]	309	58	[illegible]	130
4	40	418	[illegible]	110	[illegible]
5	40	4	63	251	184
6	40	388	52	74	10
7	40	473	90	[illegible]	23
8	[illegible]	206	81	[illegible]	118
9	42	345	6	110	[illegible]
10	44	461	92	99	4
11	4	403	[illegible]	101	137
[illegible]	46	[illegible]	[illegible]	175	43
13	47	410	65	134	119
14	49	[illegible]	2	[illegible]	[illegible]
[illegible]	49	414	81	164	38
16	49	318	58	123	67
[illegible]	49	403	81	166	85
18	51	580	65	139	16
19	51	[illegible]	110	[illegible]	110
20	1	605	116	[illegible]	72
[illegible]	51	403	67	128	36
[illegible]	[illegible]	[illegible]	56	105	[illegible]
[illegible]	[illegible]	318	119	96	43
[illegible]	57	381	8	108	6
[illegible]	[illegible]	[illegible]	130	136	96
[illegible]	58	535	134	190	94

expressed in the form of an elevation of certain serum lipoproteins, *would* characterize individuals *in advance* of the development of clinical coronary heart disease. Such evidence derived from the abnormalities in lipids in diabetes mellitus (pre-insulin period at least), in nephrosis, and in myxedema, and in a variety of familial entities—all of which are characterized by premature coronary heart disease. In all of these cases the lipid abnormality is known to precede the development of vascular disease. However, these were all special situations, and while they provided highly suggestive leads, it was essential, in dealing with the problem of coronary heart disease in the vast bulk of the population, to prove directly, as it has now been done conclusively, that the blood lipid abnormality does indeed precede the clinical development of coronary heart disease. The ability to make predictions concerning the rate of development and severity of sub-clinical coronary heart disease one to three years in advance of its conversion to clinically manifest disease is of course a major step forward. Next it is important to ask the question: Is such predictability limited to one to three years before the development of overt clinical coronary heart disease? The evidence just presented does not *limit* the predictability of future coronary disease from lipoprotein measurement to three years

TABLE IV (b)

COMPARISON OF MEAN LIPOPROTEIN LEVELS FOR 26 DE NOVO CLINICAL CORONARY DISEASE CASES WITH THOSE FOR THE AGE MATCHED POPULATION SAMPLE FROM WHICH THEY AROSE (MEN)

	Mean Age (years)	*Mean S_f 0-12 (mg/100ml)*	*Mean S_f 12-20 (mg/100ml)*	*Mean S_f 0-100 (mg/100ml)*	*Mean S_f 100-400 (mg/100ml)*
De Novo Documented Clinical Coronary Disease Group	46.6	442.2	97.[illegible]	118.3	87.3
Age Matched Healthy Population Sample out of which the coronary disease cases arose	46.6	386.0	7[illegible]	110.3	68.0
Difference (De Novo Coronary Cases—Healthy Population Sample)		+56.2	+30.1	+38.0	+19.3
		$p << 0.01$	$p << 0.001$	$p < 0.01$	$p \sim 0.05$

Rather what is meant is that such evidence by and of itself only allows assurance of the predictability for one to three years since this was the time period of the follow up study However it is possible through incorporation of other findings referable to lipoprotein levels in individuals to demonstrate that the abnormality in serum lipoproteins is undoubtedly present a much longer period than three years before the development of clinical coronary heart disease All the evidence available suggests that the lipoprotein abnormality may be used to pre select individuals who are likely to develop clinical coronary heart disease as many as ten or twenty years before the development of the overt clinical entity

In order to determine directly the maximum period before the development of clinical coronary heart disease that the lipoproteins may be used in prediction of risk of future clinical coronary heart disease it would be necessary that the follow up studies described above be carried on for five ten fifteen twenty or twenty five years These follow up studies will of course be carried on as an extension of those that have already been done However it is not necessary to await the results of the five ten fifteen or twenty year follow up periods to determine the answer of duration of predictive value since it is possible to attain this answer now The basic question underlying the problem of how long beyond three years the predictive value of lipoprotein measurement is valid is that of knowing whether people in the population tend to retain their relative positions with respect to each other in terms of lipoprotein values This point may be illustrated by considering two representative individuals in the population The data presented above would indicate that if we study one individual with high lipoprotein levels and another individual with low lipoprotein levels during the one to three year period following the lipoprotein measurement the person with high values is more likely to develop coronary heart disease than the one with low values This is true because data accumulated already have shown that the average value and the distribution of values of the lipoproteins studied in advance are higher in those who go on to develop coronary disease than in those who do not Therefore if studies had demonstrated that

the person with high lipoprotein levels had remained high for five years, and the person with low levels had remained low for five years before this study was started, then the prediction would be valid for an additional five year period This is evident since it would have been possible to determine five years earlier that the same relative position characterized the two people under consideration Similarly if instead of 5 years such consistency in *relative* position with respect to lipoprotein level had been main tained for ten or fifteen years before the study then the predic tive value would have held for this corresponding ten or fifteen year period The only situation in which the prediction avail able from the lipoprotein levels would have not been valid would arise when two individuals alter their relative positions appreci ably on the lipoprotein scale over the five ten or fifteen year period under consideration Again to settle this issue directly would require that the population of individuals be followed with serial blood sampling for a period of five ten or fifteen years of adult life Since the technical development of lipopro tein measurement is now only ten years old it has not been possi ble to follow large numbers of individuals this long However it has been possible to follow individuals at every age period in adult life for a shorter period of time That is it has been possible to study individuals at 20 years of age during a two to five year period to the age of 22 or 25 years individuals at 25 years of age to the age of 27 or 30 years individuals 30 years of age to the age of 32 or 35 years individuals at 35 years of age to the age of 37 to 40 years and so on up to the age of sixty years It has been shown that for these various spans 20 to 25 25 to 30 30 to 35 and so on up to 55 to 60 individuals tend very strongly to retain their relative ranking on the lipoprotein scale Since this has been shown to be true for every five year period between 20 and 60 years there appears to exist *no* period during adult life when individuals tend to shift around in relative positions on the lipoprotein scale Therefore it can be stated that indi viduals tend to retain their relative lipoprotein ranking in the population very well This means that the abnormality in lipo proteins which was directly proved to be predictive of coronary heart disease at least one to three years before the development

of clinical coronary heart disease can be estimated to exist in general at least for periods of the order of ten or twenty years of adult life Candidates for future clinical coronary heart disease can therefore be identified some ten to twenty years before the disease becomes overt which means that the opportunity for institution of preventive measures is excellent

There is no inference in any of these statements that the lipoprotein levels in a particular individual remain absolutely constant throughout adult life There does exist some short term fluctuation and some long term fluctuation in individuals However in general such fluctuations in levels of the crucial low density lipoproteins are small enough such that persons in the lowest 10 or 20% of the population distribution tend to remain there in spite of fluctuation whereas persons in the highest 10% of the population tend to remain there This rather than the minor fluctuations that do occur is the important issue at hand One qualification of these statements is necessary It will be shown later (Chapter IX and X) that diet and body weight are related to lipoprotein levels Therefore if an individual should significantly alter his dietary pattern and his body weight it would be expected that his relative ranking in lipoprotein levels would be altered But such dietary and weight alterations are readily determined and hence need never provide confusion concerning the person s status Similarly certain clinical entities such as nephrosis or myxedema are associated with gross alterations in lipoprotein levels Hence no surprise would be occasioned by the occurrence of a shift in relative ranking of an individual with respect to others if he should develop clinical nephrosis or myxedema

The demonstration that lipoprotein levels are elevated during the sub-clinical phase of coronary heart disease years in advance of overt clinical manifestation is beyond reasonable doubt This finding carries with it the direct implication and the information which make it possible to predict the risk of future overt clinical coronary heart disease in individuals through blood lipoprotein measurement The manner of use of the lipoprotein data for this predictive purpose and the extent of prediction possible will be elaborated in detail in Chapter V

Chapter IV

THE BLOOD PRESSURE FACTOR IN CORONARY HEART DISEASE

It is a source of amazement that at this late date there should exist so much confusion with respect to the issue of the nature of the relationship of habitual blood pressure levels with coronary heart disease both sub clinical and clinical A review of the evidence in the literature concerning the blood pressure and coronary heart disease indicates clearly that the actual data pertaining to this subject are not at all confusing but rather that the interpretation of such data has often been faulty and has led to the current divergence and haziness of authoritative views The specific problems of concern here are twofold

(a) The extent of difference if any in the habitual blood pressure in those persons developing sub clinical coronary heart disease at an excessive rate in comparison with those developing the disease at a slow rate

(b) If the habitual blood pressure is significantly related to the rate of development of sub clinical coronary heart disease it must be determined whether information is thereby provided independent of the information provided by the blood lipoprotein measurements

It is obvious why these are crucial issues in coronary heart disease For if the blood pressure is significantly related to the development of sub-clinical coronary heart disease and if the information is *independent* of the lipoprotein information then an additional tool or an additional factor is available for evaluation of any person with respect to the risk of later clinical coronary heart disease

The evidence concerning the blood pressure is derived from many sources and types of evidence Some of these sources are

indirect but have provided valuable clues crucial for a critical evaluation of the role of habitual blood pressure levels in coronary heart disease The problem at hand with respect to coronary heart disease can be stated in a frame of reference similar to that for the blood lipoproteins If one were to rank a large group of individuals in overt health upon their habitual blood pressures without any knowledge of other factors would it be true that coronary heart disease occurs with a greater frequency in those with elevated blood pressures than in those without such elevation? However before consideration of the relevant data let us review much of the ancillary evidence which can be regarded as being in the form of clues and suggestions First there is a long standing clinical impression that coronary heart disease and hypertensive cardiovascular disease are in some way related So strong has been this impression that in the minds of some physicians the two phenomena hypertension and coronary heart disease have been regarded as facets of the same problem The direct critical evidence relating these two phenomena is not nearly so good as the clinical impression would indicate Second there exists a wide spectrum of experimental data which suggests that hypertension is related to the development of arteriosclerosis of the large and medium sized arteries While evidence concerning arteriosclerosis is to be considered as suggestive it will not be made the basis of any definitive case for the findings with respect to hypertension The clinical and pathological literature show frequent recording of observations that areas of the arterial tree subjected to excessive pressure are characterized by premature and excessive degrees of arteriosclerosis One such item of evidence arises from the study of the region of the aorta before and after a coarctation Many pathology texts comment on the high degree of sclerosis in the area before the coarctation (the high pressure side) versus the much lower degree of sclerosis in the area after the coarctation (the low pressure side)[1] There also exists experimental evidence derived both from studies of the dog and of the rabbit which indicates that the blood pressure is an important factor in promoting the degree of arteriosclerosis in the arterial tree Wakerlin[19] in some critical studies in dogs performed the following experiment On one

group of dogs he performed a Goldblatt operation with constriction of the renal artery to produce a hypertension in the dog whereas on the second group he performed a sham operation without constriction of the renal artery Both groups of dogs were then maintained on an atherogenic regimen including thiouracil (for suppression of thyroid function) and the cholesterol feeding Steiner and Kendall [0] had *previously shown that in dogs this combined regimen* would produce elevation of the blood lipids and subsequent arteriosclerosis Wakerlin found that the degree of arteriosclerosis in the major arterial vessels was much greater in the group of hypertensive dogs than in the group of sham operated non hypertensive dogs even though the average extent of elevation of the blood lipids and lipoproteins was the same for the two groups of animals This represents a rather clear-cut demonstration that the elevated blood pressure was itself a major factor in promoting arteriosclerosis Similar results were obtained by Heptinstall and Porter[?1] in the study of the experimental rabbit being fed cholesterol In this case hypertension was produced by a clip on the renal artery Again it was shown by these workers that the degree of arteriosclerosis in the aorta was much more marked in the hypertensive rabbits than in the normotensive group both groups having experienced comparable blood lipid elevations

Turning now to the direct clinical evidence with respect to the relationship of hypertension with the entity of coronary heart disease rather than with arteriosclerosis one finds a vast mass of literature replete with apparently conflicting statements and opinions One statement commonly found in textbooks and in the literature is that hypertension in the female sex is a factor in coronary heart disease whereas it is not a factor in *the male* sex Another variant of this same statement is that coronary heart disease is rarely seen in a young woman unless she is a diabetic or a hypertensive It is important to examine critically the evidence which has been claimed to show the elevated blood pressure is a factor in the female sex but is not a factor in the male sex since with careful scrutiny of the data this concept is *not* supported

THE CHOICE OF CLINICAL MATERIAL FOR THE STUDY OF THE HYPERTENSION FACTOR

The basic question at hand is: Do persons with habitual elevation in blood pressure level develop *sub clinical* coronary heart disease at a greater rate than persons without such elevation? It is a corollary of this question to ask: Do persons with habitual elevation in blood pressure show a higher attack rate of *clinical* coronary heart disease than do persons without such elevation? If the answer to such questions is in the affirmative then it would be anticipated that the *average* blood pressure (measured in *advance* of the appearance of clinical coronary heart disease) will be higher for those who do develop clinical coronary heart disease in a specified time interval than for those who do not. Further it would be anticipated that there will be a shift in the distribution of blood pressures toward higher values in the group which later develops clinical coronary heart disease than in the group which does not do so in the same specified time interval. Ideally the appropriate source of clinical material for such a study is a large group of apparently healthy individuals for whom blood pressure measurements are available. Out of an adequately large group of persons there will develop a sub group with overt clinical manifestations of coronary heart disease in a one year, two year or longer period. The outgrowth of an adequately large group of subjects in the clinically overt coronary disease group during any specified follow up period is simply a matter of starting with a sufficiently large population sample in apparent health at the outset of the study. Fortunately two such studies are now available, each having yielded definitive results with respect to the issue of antecedent blood pressure elevation and coronary heart disease development. Yater has provided the data from one such study and Dawber and co workers have provided the data from another, the large scale Framingham Heart Project of the National Heart Institute. The evidence from both these studies is unequivocal and hence can provide the requisite information without recourse to any of the studies of less definitive character. However since some of less definitive studies in the clinical literature have influenced medical thinking on this subject and have led to certain highly erroneous statements

and conclusions it is important to review them here lest the physician be left with the impression that there may be controversial aspects of the problem It is important to state at the outset that *no contradictory evidence* arises from *any* of the sources of evidence The apparently contradictory conclusions represent erroneous interpretations of the clinical findings themselves

As recently as 1954 Wright Marple and Beck in their book *Myocardial Infarction* [5] *cite the work of Master Carfield and* Walters as follows These authors concluded therefore that there was no close relationship between hypertension and coronary artery disease or coronary occlusion in males less than 65 years of age Hypertension did appear however to have an important relationship with coronary occlusion in women That Wright and co workers quoted this conclusion without further comment suggests that they were not prepared to comment on its validity Indeed nowhere in their discussion of the relationship of hypertension to coronary heart disease did Wright and co authors make any definite statement of their own concerning the relationship of these entities Levine and Brown"[6] had long before stated that A pre existing hypertension is probably the most common etiologic factor in the development of myocardial infarction in the majority of cases The physician reading such reference sources might readily conclude that some question exists as to whether antecedent hypertension exists in persons who develop clinical coronary heart disease at least for men or at least for men under 65 years of age *Yet the evidence from clinical sources should not* lead to an equivocal position on this most important issue Why then does some question appear to exist?

The largest part of the confusion in the literature on this issue arises from two sources

(1) The arbitrary definition of what constitutes hypertension

(2) Having established an arbitrary definition of hypertension the clinician s expectation that some large proportion preferably over 50% of cases of myocardial infarction should have had at least this degree of antecedent hypertension

Neither an arbitrary definition of hypertension nor an

expectation that an arbitrary proportion of myocardial infarction cases would have shown antecedent hypertension by such arbitrary definition is helpful in this problem The crucial issue was outlined previously namely whether or not the myocardial infarction cases showed a distribution of antecedent blood pressures shifted to a higher level and a higher average blood pressure than persons free of clinical coronary heart disease in the same follow up period For if such a difference in average blood pressure and distribution of blood pressure values does exist then it follows unequivocally that blood pressure elevation is associated with sub clinical coronary heart disease and that the blood pressure level can be utilized as a predictive measure with respect to the development of future clinical coronary heart disease To be sure the greater the difference in the average antecedent blood pressure values between the persons who do develop clinical coronary heart disease and those who do not during the same specified time interval the more the blood pressure measurement will be helpful in prediction of the risk of future clinical coronary heart disease for currently healthy persons But no statistical or medical consideration justifies the requirement that any arbitrary proportion of the de novo myocardial infarction cases exceed any arbitrary blood pressure level When analyzed correctly every reported study known to the present author clearly supports the view that antecedent blood pressure elevation is distinctly associated with the development of sub-clinical coronary heart disease and that the blood pressure is an important predictive measure in determination of the risk of future clinical coronary heart disease for *both men and women at all ages* While some of the reported studies utilized clinical material of somewhat doubtful value the evidence from them as a whole is so overwhelming as to leave no doubt about the findings and their proper interpretation The chief criticism of the usual clinical material is that the cases of myocardial infarction are either from hospital admissions or from the office practise of the reporting physician In these studies some authors utilized antecedent blood pressure measurements for such cases either from their own office records or from hospital charts The doubt we must entertain centers around the very fact that a measurement

and conclusions it is important to review them here lest the physician be left with the impression that there may be controversial aspects of the problem It is important to state at the outset that *no contradictory evidence* arises from *any* of the sources of evidence The apparently contradictory conclusions represent erroneous interpretations of the clinical findings themselves

As recently as 1954 Wright Marple and Beck in their book *Myocardial Infarction* [4] cite the work of Master Garfield and Walters as follows These authors concluded therefore that *there was no close relationship between hypertension and coronary* artery disease or coronary occlusion in males less than 65 years of age Hypertension did appear however to have an important relationship with coronary occlusion in women That Wright and co workers quoted this conclusion without further comment *suggests that they were not prepared to comment on its validity* Indeed nowhere in their discussion of the relationship of hypertension to coronary heart disease did Wright and co authors make any definite statement of their own concerning the relationship of these entities Levine and Brown [6] had long before stated that A pre existing hypertension is probably the most common etiologic factor in the development of myocardial infarction in the majority of cases The physician reading such reference sources might readily conclude that some question exists as to whether antecedent hypertension exists in persons who develop clinical coronary heart disease at least for men or at least for men under 65 years of age Yet the evidence from clinical sources should not lead to an equivocal position on this most important issue Why then does some question appear to exist?

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Neither an arbitrary definition of hypertension nor an

persons taken as representative of the population at large by the same criteria of blood pressure limits (160 mm Hg systolic or 100 mm Hg diastolic or both) such a group of persons at age 58.5 years would be expected to show 28 to 30% with a classification of hypertension Since Levine and Brown found 40% of their patients to qualify (plus additional cases with *clinical* evidence of pre-existing hypertension) it is clear that in this series the mean blood pressure was high and the distribution of values shifted toward high levels in the persons experiencing myocardial infarction as compared with the population at large

Rathe[7] analyzed the history in 274 cases of myocardial infarction In this group were 194 men (average age 58.9 years) and 80 women (average age 59.7 years) Of the entire group 173 patients or 63% were known to have had blood pressures of over 140 mm Hg systolic or 90 mm Hg diastolic or both antecedent to their coronary occlusion Since the antecedent blood pressure was not known for many patients the true incidence of pressures above these limits must have been greater than the 63% recorded by Rathe From the Master data it would be anticipated that approximately 57% of individuals of this average age would show blood pressures of over 140 mm Hg systolic or 90 mm Hg diastolic or both Since the Rathe incidence of 63% is a *minimum* value it appears that his series of patients with clinical coronary heart disease had had antecedent elevation of blood pressures in comparison with those in the population at large

Chambers[7] reported on a series of 100 cases of myocardial infarction (72 males and 28 females) For 85 of these 100 cases the blood pressure during *the pre infarction* period was known As criteria for hypertension he required a systolic pressure of 150 mm Hg or more plus a diastolic pressure of 90 mm Hg or more Seventy four of the 100 cases were known to have been hypertensive by these criteria while for 15 cases the antecedent blood pressure was unknown Therefore *at a minimum* 74% of his cases were hypertensive before the myocardial infarction From the Master data utilizing the criterion of diastolic pressure 90 mm Hg or higher no more than 35% of the population at large would be hypertensive (and this is a *less* rigid criterion than that of Chambers) Therefore the 100 case series of Chambers showed a strik

of the blood pressure for such persons *exists*, especially when we wish to compare such blood pressures with those in the population at large For if a person has a hospital chart record or an office record of previous blood pressure readings there must have existed some medical complaint that had led him either to a physician s office or to a hospital, unless he were accustomed to routine periodic medical check ups Thus the possibility that such blood pressures are not representative of those in the population at large definitely exists, and indeed they may be seriously biassed in the direction of elevated pressures On the other hand in some of the reported series of cases antecedent blood pressure records were unavailable for some of the cases of myocardial infarction In such cases the authors utilized blood pressure readings taken on the patients during their hospitalization for the myocardial infarction itself This type of blood pressure reading will for many cases be lower than the habitual blood pressure the particular person would have shown in the months or years before myocardial infarction since it is well known that the blood pressure may fall appreciably (and remain low for a long period) after myocardial infarction Numerous of the workers were cognizant that in hospital blood pressures might be biassed and biassed in the direction of being too low as a measure of the particular patient s habitual blood pressure Thus some possible sources of bias exist that might yield too high a blood pressure for the cases of clinical coronary heart disease whereas others exist that might yield too low a blood pressure *To what extent* such biasses cancel each other out in some of the studies reported in the literature is problematical However with the necessary reservations in mind it is worthwhile to consider the major literature reports on the relationship of blood pressure levels with myocardial *infarction both in men and women at various ages*

Levine and Brown studied 145 patients with myocardial infarction Of this group of patients 58 were known to have had pre existing hypertension, using as a definition of hypertension a systolic pressure of 160 mm Hg or more or a diastolic pressure *of 100 mm Hg or more The average age for this group* of patients was 58 5 years From the data of Master Garfield and Walters based upon the analysis of data for 74 000 employed

persons taken as representative of the population at large by the same criteria of blood pressure limits (160 mm Hg systolic or 100 mm Hg diastolic or both) such a group of persons at age 58 5 years would be expected to show 28 to 30% with a classification of hypertension Since Levine and Brown found 40% of their patients to qualify (plus additional cases with *clinical* evidence of pre-existing hypertension) it is clear that in this series the mean blood pressure was high and the distribution of values shifted toward high levels in the persons experiencing myocardial infarction as compared with the population at large

Rathe[7] analyzed the history in 274 cases of myocardial infarction In this group were 194 men (average age 58 9 years) and 80 women (average age 59 7 years) Of the entire group 173 patients or 63% were known to have had blood pressures of over 140 mm Hg systolic or 90 mm Hg diastolic or both antecedent to their coronary occlusion Since the antecedent blood pressure was not known for many patients the true incidence of pressures above these limits must have been greater than the 63% recorded by Rathe From the Master data it would be anticipated that approximately 57% of individuals of this average age would show blood pressures of over 140 mm Hg systolic or 90 mm Hg diastolic or both Since the Rathe incidence of 63% is a *minimum* value it appears that his series of patients with clinical coronary heart disease had had antecedent elevation of blood pressures in comparison with those in the population at large

Chambers [7] reported on a series of 100 cases of myocardial infarction (72 males and 28 females) For 85 of these 100 cases the blood pressure during the pre infarction period was known As criteria for hypertension he required a systolic pressure of 150 mm Hg or *more plus* a diastolic pressure of 90 mm Hg or more Seventy four of the 100 cases were known to have been hypertensive by these criteria while for 15 cases the antecedent blood pressure was unknown Therefore at a *minimum* 74% of his cases were hypertensive before the myocardial infarction From the Master data utilizing the criterion of diastolic pressure 90 mm Hg or higher no more than 35% of the population at large would be hypertensive (and this is a *less* rigid criterion than that of Chambers) Therefore the 100 case series of Chambers showed a *strik*

ing elevation in blood pressure and a shift to higher values as compared with the population at large

Doscher and Poindexter[8] reported a series of 414 cases of myocardial infarction observed between 1935 and 1948 including 334 men and 80 women As a criterion for hypertension they required a *history of or an observation post infarction* of a diastolic pressure of 100 mm Hg or more Since no history was available for some of the cases and because infarction itself can have lowered observed post infarction pressures the incidence of hypertension reported by Doscher and Poindexter would have to be regarded as a minimum value Since sufficient numbers of cases are available for several age categories for both sexes comparisons are made in Table V between the hypertension incidence in the Doscher Poindexter series and the population at large data of Master For each age category and for both sexes the Doscher Poindexter series shows a striking shift of blood pressures to high values in those persons developing myocardial infarction in comparison with the persons in the population at large

Mintz and Katz [9] reported a series of 572 cases of myocardial infarction from the 1940 1945 experience at Michael Reese Hospital For 308 of these cases the blood pressure values in the pre infarction period were known Of this latter group 188 cases (61%) were known to have had diastolic blood pressures above 90 mm Hg The average age of the males in their series was 59 2 years the average age of the females was 62 2 years From the distribution of males and females in their series and the incidence of hypertension for the two sexes it is readily calculated that approximately 50% of the men and 86% of the women had antecedent hypertension by their criterion These values should be compared as follows with the analogous data of Master for the population at large the 50% of men with coronary disease with a value of 35% for men in the population at large the 86% of women with coronary disease with a value of 39% for women in the population at large Clearly for both sexes the Mintz and Katz series of cases of myocardial infarction shows a marked shift to high values of the blood pressure for persons later experiencing myocardial infarction

Master Garfield and Walters presented data for 554 cases of

TABLE VI

INCIDENCE OF HYPERTENSION BY AGE AND SEX IN DOSCHER POINDEXTER SERIES OF MYOCARDIAL INFARCTION CASES

(Criterion of Hypertension Diastolic Pressure 100 mm Hg or Higher)

Males	30 39 Years	40 49 Years	50 59 Years	60-69 Years	70+ Years
Number of cases	(18 cases)	(85 cases)	(176 cases)	(85 cases)	(90 cases)
Incidence of Hypertension in Myocardial Infarction Cases	11	29%	33%	42%	55%
Incidence of Hypertension in Population at large (Matched by age)	3	[illegible]	11	15%	Data not available
Females					
Number of cases	(1 case)	(3 cases)	(55 cases)	(97 cases)	(14 cases)
Incidence of Hypertension in Myocardial Infarction Cases	Too few cases	Too few cases	51%	41%	61%
Incidence of Hypertension in Population at large (Matched by age)			1 %	16%	Data not available

Population at large data are those of Master Garfield and Walters[26]

coronary occlusion in whom the status of antecedent blood pressures was evaluated By Master s method hypertension is defined for any age and sex group as that blood pressure value exceeded only by 2 5% of the persons in the population at large Therefore in comparing his infarction series with the population at large the incidence of hypertension in the latter group by his criteria is always 2 5% The comparison of Master s infarction series with the population at large is presented in Table VI In both sexes and for every age category where adequate data are available there is a strikingly greater incidence of hypertension in the myo

TABLE VI

Incidence of Antecedent Hypertension in Myocardial Infarction Cases
(Based upon 554 Cases of Master and Co-workers[31])

Males Age Group	*Number of Cases of Myocardial Infarction*	*Incidence of Hypertension in Myocardial Infarction Cases (%)*	*Incidence of Hypertension in Population at Large* (%)*
35-39 years	18	16.7%	2.5%
40-44 years	66	25.8%	2.5%
45-49 years	80	27.5%	2.5%
50-54 years	121	28.9%	2.5%
55-59 years	105	25.6%	2.5%
60-64 years	61	31.2%	2.5%
Females			
35-39 years	4	75.0%	2.5%
40-44 years	9	44.4%	2.5%
45-49 years	9	7[illegible]6%	2.5%
50-54 years	18	77.8%	2.5%
55-59 years	28	64.4%	2.5%
60-64 years	32	78.2%	2.5%

* All values for the incidence of hypertension in the population at large are necessarily 2.5% in this tabulation by virtue of Master's definition of hypertension.

cardial infarction cases than in the corresponding group from the population at large. Master, however, focussing on another aspect of the data, drew the opposite conclusion. He pointed out that hypertension (by his definition) was present *only* in 27% of the males. Since this meant that over 70% of men with coronary occlusion had had normal blood pressures, he stated, "The evident conclusion to be drawn is that there is no very close relationship between hypertension and coronary artery disease and occlusion in the males, at least in those under sixty-five years of age." The really correct evident conclusion is that elevation in blood pressure is *strongly* related to development of coronary occlusion in men at every age investigated. When 27% of the persons who *develop coronary occlusion are characterized by blood pressures* above a specified level in contrast with 2.5% of the persons who do not develop coronary occlusion in the same time period, we have at hand a fabulously strong association between coronary occlusion and antecedent elevation in blood pressure. The error in Master's reasoning lies in choosing an arbitrary blood pressure value (that above which lie only 2.5% of the population) and then

being disturbed by the fact that only 27% of the coronary occlusion cases had antecedent pressures above this level The real comparison is between 27% and 2 5% rather than between 27% and 100%

While it is clear from these several clinical series of myocardial infarction cases that antecedent blood pressure elevation characterizes persons developing clinical coronary heart disease there remain the possible sources of bias described previously We may therefore consider the evidence from two studies where such sources of bias do not exist One such study the Framingham study of the National Heart Institute has recently been reported by Dawber Moore and Mann [3] This is a continuing epidemiological study of the extent of development of new cardiovascular disease in a cross section of the population of the town of Framingham Massachusetts All the subjects in this cross section of the population are examined by clinical and laboratory methods every two years and a careful followup is in progress continually to ascertain the development of such new events as myocardial infarction or other forms of coronary heart disease The experience with four years of follow up in this study yielded definitive results with respect to the relationship of blood pressure with the subsequent evolution of clinical coronary heart disease There were 898 men between the ages of 45 and 62 years who represented the population at risk during the reported four year follow up period At the time of the initial examination none of these 898 men showed evidence clinical or laboratory of definite coronary heart disease During the four year period 48 of the men developed what were regarded as definite manifestations of clinical coronary heart disease including one or more of the following entities myocardial infarction coronary occlusion angina pectoris myocardial fibrosis or electrocardiographic evidence of myocardial infarction The original group of 898 men can be subdivided on the basis of blood pressure into two major groups the normotensives on initial examination and those with varying degrees of hypertension borderline or definite For purposes of definition of normotension Dawber and co-workers used the criterion that left arm blood pressures had to be below 140/90 mm Hg on independent observations by two physicians All other

subjects fit into one or another category such as borderline hyper tension definite hypertension and possible or definite hyperten sive heart disease The normotensive group constituting 310 men developed 8 cases of new events classified as manifestations of clinical coronary heart disease during the four year follow up period * The remaining group (various degrees of hypertension by their criteria) constituting 541 men, developed 40 cases of new events classified as manifestations of clinical coronary heart disease during the four year follow up period Thus for the normoten sive group the incidence rate of de novo clinical coronary heart disease was 26 *cases per 1000 persons at risk over the four year* period whereas for the hypertensive group the incidence rate of de novo clinical coronary heart disease was 74 cases per 1000 per *sons at risk over the same time period* *This difference in attack* rates of de novo clinical coronary heart disease is significant and clearly supports the concept that elevation in blood pressure increases the risk of future clinical coronary heart disease Stated otherwise this evidence links elevation in blood pressure with the *sub clinical* phase of coronary heart disease and indicates that the blood pressure is one predictive measure for ascertaining the risk a person carries for passing from the sub clinical to the clinical phase of coronary heart disease

Another wholly separate study provides evidence completely consistent with that derived from the Framingham study This is the analysis of Yater and co workers - of 542 men who survived a documented myocardial infarction or who died of coronary heart disease while in the Armed Services The average age of this group was approximately 33 years For these men who developed their clinical coronary heart disease while in the Armed Service there was available to Yater the blood pressure values at induction examination at which time all the men were free of recognizable clinical coronary heart disease In order to have a control group whose blood pressures had been measured under as nearly identi cal conditions as for the coronary heart disease group Yater util ized the induction blood pressures for 213 men who were service connected amputees or who were otherwise wounded none of

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Forty seven of *the 898 men were normotensive* but had a history of cerebro vascular accident of rheumatic heart disease These are excluded from analysis

whom had overt coronary heart disease The systolic pressures were found to be above normal (utilizing a criterion of 139 mm Hg systolic as the upper limit of normal) in 27 9% of the men (18 to 39 years of age) who subsequently developed clinical coronary heart disease contrasted with 8 9% of the men in the Army control group Thus there was a three fold increase in the incidence of high systolic pressures at Army induction for those who subsequently developed clinical coronary heart disease in comparison with those who did not The same type of trend was evident for the diastolic blood pressures Whereas 19 1% of the men who subsequently developed clinical coronary heart disease had shown diastolic blood pressures above 90 mm Hg at induction only 3 8% of the Army control group had shown diastolic pressures above 90 mm Hg at induction There was therefore a five fold increase in incidence in prior diastolic blood pressure elevation above 90 mm Hg in the coronary disease group in comparison with the control group Clearly the Yater data indicate that elevation both in systolic and diastolic blood pressures characterizes the men in the 18 39 year age group who go on to develop clinical coronary heart disease in comparison with those men of the same age group who remain free of overt clinical coronary heart disease during the same time period

The combination of the Framingham evidence with Yater s evidence covers the age span for men from 18 to 62 years of age Over this entire age span the relationship between antecedent blood pressure elevation and later development of clinical coronary heart disease is known to be valid *Yet this is essentially* the age span in men for which Master had concluded that there was no close relationship between hypertension and the subsequent development of clinical coronary heart disease No contradiction whatever exists among the findings of Dawber at Framingham of Yater in the Army and of Master in his series All show that blood pressure elevation is associated with a sizably higher attack rate of future clinical coronary heart disease Master s difficulty resided in his expectation that an *arbitrarily* large percentage of men who subsequently develop clinical coronary heart disease must have a blood pressure elevation of *arbitrary* degree if the blood pressure is to be important No real justifi

subjects fit into one or another category such as borderline hyper tension definite hypertension and possible or definite hyperten sive heart disease The normotensive group constituting 310 men developed 8 *cases of new events classified as manifestations of* clinical coronary heart disease during the four year follow up period * The remaining group (various degrees of hypertension by their criteria) *constituting 541 men developed 40 cases of new* events classified as manifestations of clinical coronary heart disease during the four year follow up period Thus for the normoten sive group *the incidence rate of de novo clinical coronary heart* disease was 26 cases per 1000 persons at risk over the four year period whereas for the hypertensive group the incidence rate of de novo clinical *coronary heart disease was 74 cases per 1000 per* sons at risk over the same time period This difference in attack rates of de novo clinical coronary heart disease is significant and clearly supports the concept that elevation in blood pressure increases the risk of future clinical coronary heart disease Stated otherwise this evidence links elevation in blood pressure with the *sub clinical* phase of coronary heart disease and indicates that the blood pressure is one predictive measure for ascertaining the risk a person carries for passing from the sub clinical to the clinical phase of coronary heart disease

Another wholly separate study provides evidence completely consistent with that derived from the Framingham study This is the analysis of Yater and co workers of 542 men who survived a documented myocardial infarction or who died of coronary heart disease while in the Armed Services The average age of this group was approximately 33 years For these men who developed their clinical coronary heart disease while in the Armed Service there was available to Yater the blood pressure values at induction examination at which time all the men were free of recognizable clinical coronary heart disease In order to have a control group whose blood pressures had been measured under as nearly identi cal conditions as for the coronary heart disease group Yater util ized the induction blood pressures for 213 men who were service connected amputees or who were otherwise wounded none of

*Forty seven of the 898 men were normotensive but had a history of cerebro vascular accident of rheumatic heart disease These are excluded from analysis

Whatever the merits of this possible explanation for the association of elevation in blood pressure with a higher frequency of clinical coronary heart disease it has contrary to many opinions no bearing upon the utility of the blood pressure measurement as a predictive measure in assessing the risk of future clinical coronary heart disease The data reviewed in this chapter establish conclusively that the average elevation in blood pressure is present *during the sub clinical* phase of coronary heart disease and for a period of several years *before* the evolution of clinically-overt coronary heart disease This is the crucial issue with respect to the question of utility of the blood pressure as a *predictive* criterion Whether the blood pressure is a factor in acceleration of the coronary disease or whether the coronary disease results in the blood pressure rise as a compensatory mechanism the existence of the pressure elevation during the sub clinical phase of coronary heart disease *necessarily* means that the measurement of blood pressure is of value in assessing the development of coronary heart disease and hence the risk of serious future clinical consequences The possibility of prevention or therapy of coronary heart disease is of course a matter apart from such considerations If the blood pressure elevation is truly part of a compensatory mechanism to increase coronary artery blood flow then efforts to lower blood pressure as a means of preventing or treating coronary heart disease would be unwise On the other hand if the blood pressure elevation is a predisposing factor to coronary heart disease there would exist excellent justification for attempting to lower the blood pressure in the effort to prevent or treat clinical coronary heart disease This question cannot be decided from the observation of the association of sub-clinical coronary heart disease with blood pressure elevation Direct clinical preventive and therapeutic experiments are necessary supplements toward this end However all the indirect evidence supports the view that the blood pressure elevation accelerates the development of the coronary heart disease rather than that the coronary heart disease causes the elevation in pressure The experimental animal data point very strongly to the probability that the way in which blood pressure elevation comes to be associated with coronary heart disease is

cation exists for such a view The extent of the differences in attack rate of clinical coronary heart disease for persons with high blood pressure versus those with low blood pressure is in reality quite phenomenal and provides predictive information of major value Exactly how these differences are to be utilized in the advance prediction of future clinical coronary heart disease will be detailed in Chapter V

To be sure the data from all the sources of evidence show clearly that blood pressure values above some arbitrary high level are not *prerequisite* to the development of clinical coronary heart disease Clinical coronary heart disease *can* and *does* develop in persons with moderate or even low blood pressures but the frequency of its occurrence is strikingly lower than in persons with elevation in blood pressure Perhaps another feature which *Master found disturbing was that antecedent elevation in blood* pressure is much more frequently found in women who develop clinical coronary heart disease than in men who do so This finding in no way negates the importance of the blood pressure level for the development of clinical coronary heart disease in men at any age There exist good and sufficient reasons why hypertension should be expected to be a more frequent finding among women who develop clinical coronary heart disease than among men who develop this disease The explanation of this phenomenon requires consideration of the blood pressure findings together with the lipoprotein findings and the manner in which risk of coronary heart disease is related to both factors operating simultaneously Therefore detailed consideration of the difference in incidence of hypertension between men and women who develop coronary heart disease is presented in Chapter VIII, where such risk calculations are explained

There are some writing on the subject of coronary heart disease who raise the question as to whether the elevation in blood pressure observed in those who go on more frequently to develop clinical coronary heart disease may not be a protective phenomenon Thus Yater suggested the possibility that the hypertension which precedes clinical coronary heart disease may be part of an effort to compensate for reduced coronary arterial *blood flow by an increase in the pressure in the* arterial tree

viduals at a particular age are evaluated both with respect to lipoprotein levels and blood pressure levels and then followed for a period of years a sub group will develop which shows clinically manifest coronary heart disease This sub group we now know would have originally been characterized both by elevation in lipoprotein levels and in blood pressure levels From the extent of correlation of blood lipoprotein levels and blood pressure levels it can be calculated that a certain blood pressure elevation would be expected in the sub group with clinical coronary heart disease even if the blood pressure provided *no* independent predictive information However direct test of such evidence by the author and his colleagues[1] showed that there is an elevation of blood pressure *over* and *above* that expected from the correlation of blood lipoproteins and blood pressure Hence the blood pressure *does* provide information of predictive value concerning future clinical coronary heart disease *in addition* to that provided by lipoprotein analysis An alternative manner of considering the test for independence may be described If the sub-group which does develop clinical coronary heart disease is matched with random cases from the population at large such that the lipoprotein levels are equivalent for both groups is the blood pressure *still* elevated in the group with clinical coronary disease in comparison with the lipoprotein matched controls? Direct test of this showed that the blood pressures were still elevated in the coronary disease group even when the two groups were matched upon lipoprotein levels This *is* clear evidence that the blood pressure measure provides information additional to and independent of that provided by lipoprotein measurement Hence in any consideration of risk of future clinical coronary heart disease both factors blood lipoprotein level and blood pressure level must be evaluated or valuable information will necessarily be lost

via the effect of hypertension in acceleration of the coronary arteriosclerotic process The increased arteriosclerosis in humans in regions of the vascular tree subjected to excessive pressure is consistent with the animal data and not at all supportive of the concept that the blood pressure elevation is a compensatory phenomenon Altogether the indirect evidence suggests that the blood pressure elevation in addition to being predictive of clinical coronary heart disease by virtue of its statistical association with it in all likelihood abets the development of coronary heart disease

INDEPENDENCE OF THE INFORMATION PROVIDED BY THE BLOOD PRESSURE

In Chapter III it was shown that conclusive evidence is available to show that the blood low density lipoproteins are on the average elevated during the sub-clinical phase of coronary heart disease and hence blood lipoprotein measurements have predictive implications for future clinical coronary heart disease In this chapter it has been shown that similar conclusive evidence is at hand that information of predictive value for clinical coronary heart disease is obtained through the measurement of the blood pressure of persons in advance of any overt manifestations of coronary heart disease Do these two sets of measurements provide *independent* information concerning the risk of future clinical coronary heart disease? If *no* independent information were provided by blood pressure measurement over and above that provided by lipoprotein measurement this would mean that any predictive information from blood pressure measurement must have arisen solely through a correlation of elevation of blood pressure with elevation in blood lipoprotein levels In this case the blood pressure measurement would be of no predictive value for future clinical coronary heart disease once the lipoprotein levels were known There does indeed exist a low order correlation between lipoprotein levels and blood pressure levels However this is not sufficient evidence upon which to base the decision as to whether the blood pressure measurement provides *independent* predictive information The critical test for this point is made in the following manner If a large group of indi

develop clinical coronary heart disease in some specified time interval there simply are not enough data available today to make this sort of exact evaluation However what information is available makes for a tremendous amount of predictive power a power that can be used now in a sensible program designed for the prevention of coronary heart disease

For illustrative purposes in the demonstration of how risk is directly related to the measurement of any particular variable that is elevated in those individuals going on to develop clinical coronary heart disease compared with the population out of which they arise the data concerning the S_f0 12 lipoprotein measurement in 40-49 year old men will be utilized here Also because the data are available for a much larger number of cases the S_f0 12 measurement for a large series of cases with documented clinical coronary heart disease will be used instead of the smaller series of de novo cases of myocardial infarction arising in previous well individuals This is perfectly justifiable since the levels of the various lipoprotein classes characterizing the de novo cases of myocardial infarction were shown in a previous discussion (page 57) to be quite comparable with those characterising cases with already established clinical coronary heart disease Available also are the distributions of the S_f0 12 lipoproteins in age and sex matched controls from the population at large If the coronary cases had arisen out of a large series of such age and sex matched controls in overt health we would have the S_f0 12 distribution of values for the original population sample and the values which characterize those individuals who became cases of clinical coronary heart disease at some future time whatever that time might be e g 1 year 2 years or 3 years later Listed in Table VII is the distribution of S_f0 12 values assuming a base population of 10 000 subjects evaluated Actually this distribution was determined on 525 subjects and simply multiplied by a conversion factor to calculate what the numbers would be in each S_f0 12 lipoprotein category for an over all group of 10 000 subjects One has therefore in Table VII for each small range of S_f0 12 values a number which represents the number of individuals found in the population at large who would show this S_f0 12 lipoprotein value upon measurement As is to be expected most of

Chapter V

THE PREDICTION OF FUTURE CLINICAL CORONARY HEART DISEASE

EVIDENCE is available which indicates conclusively that two independent factors characterize the individual developing excessive sub clinical coronary heart disease These are the level of certain blood lipoproteins and the level of the diastolic blood pressure Both for the lipoprotein level and the blood pressure it *has been proven beyond reasonable doubt that the abnormality* manifests itself during the sub clinical phase of coronary disease namely before the evolution of the disease into the clinically overt state How is this information to be used in the prediction of clinical coronary heart disease risk in otherwise healthy individuals? It can be readily demonstrated through simple arith *metic that when a measurement (any measurement) shows* a higher average value and a shift in the distribution to higher values for those individuals who later go on to develop clinical coronary heart disease such a measurement is directly capable of being translated into a prediction of the risk of future clinical coronary heart disease At the outset it must be emphasized vig orously that what can be predicted is the *risk* of future clinical coronary heart disease Much confusion needlessly centers around this point There is no intent to state or claim that pre diction is possible for a particular individual that he *will* develop clinical coronary heart disease in any specified time interval This would not be a risk but a forecast of future certainty By risk is meant the probability or likelihood of developing coro nary heart disease rather than the certainty involved in naming the day or year a particular individual will develop coronary heart disease While the physician might like to have unequivocal information concerning whether or not a particular subject will

of our base population for which a risk calculation can be made. If there are 31 cases of coronary disease below the median value arising out of 5000 individuals, this is a coronary disease attack rate of 6.2 per thousand individuals. On the other hand, since there are 82 cases of clinical coronary disease arising out of the 5000 individuals with levels above the median value, this represents an attack rate of 16.4 per thousand, which is 2.65 times as high as the value for the segment of the base population below the median value. Therefore *without any further information* concerning such individuals it is possible to state that if a person is measured with respect to S_f0-12 lipoprotein level and if his level is above the median value, he is 2.65 times as likely to develop clinical coronary heart disease in some specified time interval as he would be had his S_f0-12 lipoprotein level been below the median value. It is to be remembered that this statement holds when such other variables as age and sex are matched. There is no inference that prediction would be handled in this simple manner if a 20 year old man were to be compared with a 65 year old woman. The problem of dealing with the age and

TABLE VIII

DISTRIBUTION OF S_f0-12 LIPOPROTEIN LEVELS IN 113 CASES OF DOCUMENTED MYOCARDIAL INFARCTION (MEN, AGE 40-49 YEARS)

Range of S_f0-12 Lipoprotein Levels mg/100 ml	*Number of Men in Each S_f0-12 Category*
Less than 224	2
224-267	4
268-311	6
312-356	10
357-401	16
402-446	24
447-491	24
492-535	15
536-580	8
581 or higher	4
TOTAL GROUP	113

Median S_f0-12 Lipoprotein Level = 456 mg/100ml

the individuals show values near the median for the S_f0 12 lipo protein level for 40-49 year old males (average age = 44 5 years) which is 381 mg/100ml Listed in Table VIII is the correspond ing distribution of S_f0 12 lipoprotein levels for the 113 cases of clinical myocardial infarction which can be said to have developed out of a population comparable to that shown in Table VII in a time period such as two to three years The simplest approach to translation of these two tables of values into predictive terms would be to consider values above and below the median value of the S_f0 12 lipoproteins for the base population For this base population of 10 000 persons the definition of the median value implies that there will be 5000 individuals with S_f0 12 lipopro tein levels above that value and 5,000 individuals with levels below that median value If we now direct attention to the cases of myocardial infarction arising out of such a base popula tion and total up the number of cases below this same median value of 381 mg % we find there are 31 values below this level and 82 values above this level Therefore we have a two fold split

TABLE VII

DISTRIBUTION OF S_f0 12 LIPOPROTEIN LEVELS IN AN OVERTLY HEALTHY BASE POPULATION OF 10 000 MEN (AGE 40 49 YEARS)

Range of S_f0 12 Lipoprotein Levels (mg/100ml)	*Number of Men in Each S_f0 12 Category*
Less than 224	362
224 267	476
268 311	1143
312 356	1791
357 401	2115
402-446	1980
447 491	1372
492 535	514
536 580	171
581 or higher	76
TOTAL GROUP	10 000

Median S_f0 12 Lipoprotein Level = 381 mg/100ml
S_f0 12 Level separating lowest from second lowest quarter of group = 327 mg/100ml
S_f0 12 Level separating third quarter from highest quarter of group = 439 mg/100ml

process further allows the construction of a table of 10 individual categories relating risk of future clinical coronary heart disease to S_f0 12 lipoprotein levels Such a risk evaluation for various S_f0 12 lipoprotein levels is presented in Table IX where the risk for the lowest S_f0 12 level is arbitrarily set at 1 0 and where all other risk values are expressed in comparison with this value Without any further information about the persons involved such a table can be used to determine the relative risk of one individual versus another developing future clinical coronary heart disease in a specified time interval Many misleading statements have emanated from some writers who have stated that this type of risk information holds true for groups but does not apply to the individual Such reasoning is entirely erroneous A risk is a value that has meaning *for an individual* The error arises from the fact that some persons are confusing the *risk* of future clinical coronary heart disease with an absolute statement of the day week or month that this particular individual will develop clinical coronary heart disease Let us review what is meant by risk Suppose that two groups each constituting one thousand individuals are considered the first group all having S_f0 12 lipoprotein levels of 200 mg/100ml and the second group

TABLE IX

RELATIVE RISK OF MYOCARDIAL INFARCTION AT VARIOUS S_f0 12 LIPOPROTEIN LEVELS

S_f0 12 Lipoprotein Level (in mg/100ml)	*Relative Risk of Development of Myocardial Infarction (All risks referred to the risk at 200 mg/100ml S_f0 12 lipoproteins set at 1.00)*
200	1 00
250	1 06
300	1 15
350	1.2[illegible]
400	1.50
4[illegible]0	2 30
500	3 90
5 0	6.30
600	9 75
6 0	13.2

the sex factors will be considered later (Chapters VII and VIII)

It is quite evident that such a two fold prediction table can readily be extended There is no reason to limit sub-division of the base population with respect to standard S_f0 12 level to just a two fold split above and below the median value The base population can be sub divided still further into the lowest quarter the next quarter the third quarter and the highest quarter of the group of individuals with respect to S_f0 12 levels yielding 2500 individuals in each of the four categories The S_f0 12 lipoprotein level that separates the lowest quarter from the second lowest quarter is *327 mg/100ml the level that separates the* third quarter from the highest quarter is 439 mg/100ml and the median value 381 mg/100ml separates the two intermediary quarters From the overall group of cases of coronary disease *those with S_f0 12 lipoprotein levels below the value separating* the lowest quarter from the second lowest quarter come to 14 cases In the second lowest quarter there are 17 cases, in the third quarter there are 25 cases and in the highest quarter there are 57 cases Now it is possible to compare the risk of future clinical coronary heart disease for individuals in any one quarter with the risk for individuals in any other quarter If in the lowest quarter there are 14 cases arising out of 2500 people then the coronary disease attack rate is 5 6 cases per thousand persons at risk for the second quarter the rate is 6 8 per thousand for the third quarter the rate is 10 0 per thousand and for the highest quarter the rate is 22 8 per thousand Comparison of the attack rate for any quarter with that for any other quarter provides immediately the relative risk of future clinical coronary heart disease carried by persons in these categories simply on the basis of S_f0 12 lipoprotein levels

It is quite evident that with respect to the S_f0 12 lipoprotein measurement the base population could have been sub divided into ten segments each representing an interval of *S_f0 12 lipoprotein levels from the lowest ten percent of the population* up through to the highest ten percent Then by counting the number of cases of clinical coronary disease in each such segment calculation of the number of cases per thousand persons at risk for each segment *is readily possible* Carrying such a

process further allows the construction of a table of 10 individual categories relating risk of future clinical coronary heart disease to S_f0 12 lipoprotein levels Such a risk evaluation for various S_f0 12 lipoprotein levels is presented in Table IX where the risk for the lowest S_f0 12 level is arbitrarily set at 1 0 and where all other risk values are expressed in comparison with this value Without any further information about the persons involved such a table can be used to determine the relative risk of one individual versus another developing future clinical coronary heart disease in a specified time interval Many misleading statements have emanated from some writers who have stated that this type of risk information holds true for groups but does not apply to the individual Such reasoning is entirely erroneous A *risk* is a value that has meaning *for an individual* The error arises from the fact that some persons are confusing the *risk* of future clinical coronary heart disease with an absolute statement of the day week or month that this particular individual will develop clinical coronary heart disease Let us review what is meant by risk Suppose that two groups each constituting one thousand individuals are considered the first group all having S_f0 12 lipoprotein levels of 200 mg/100ml and the second group

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S_f0 12 Lipoprotein Level (in mg/100ml)	*Relative Risk of Development of Myocardial Infarction (All risks referred to the risk at 200 mg/100ml S_f0 12 lipoproteins set at 1.00)*
200	1.00
250	1 06
300	1 15
3 0	1.22
400	1.50
450	2 30
500	3 90
5 0	6.30
600	9 75
6 0	13.2

all having S_f0-12 lipoprotein levels of 500 mg/100ml The data in Table IX indicate that the relative risk of future coronary heart disease for members of the high group is 3 90 times that of the low group What this means is that if the 1000 individuals with low S_f0-12 lipoprotein values and the thousand individuals with the high S_f0-12 values were in apparent clinical health (which means that they are in the sub-clinical phase of coronary heart disease) and if both groups were observed for a time period such as two years clinical coronary heart disease would develop in some members of both groups If out of the thousand individuals with the lowest S_f0-12 levels there developed 10 cases of clinical coronary heart disease then the relative risk table means that out of the group of 1000 individuals with the high S_f0-12 levels there would be 3 90 times ten or 39 cases of clinical coronary heart disease Obviously it is true that even for the group with high lipoprotein levels *most* individuals do not develop clinical coronary heart disease in a short specified time interval such as two years but this represents no erroneous diagnosis of the *risk* for such persons No false assessment of a person s chance of development of coronary heart disease is represented by this fact It is simply inherent in the nature of a risk calculation that many persons will escape the disease even though they are individually characterized by a very high risk of such disease compared with other persons

In an entirely analogous manner one could treat the S_f12-20 lipoprotein measurement to calculate a coronary heart disease risk value that corresponds with each and every level of the S_f12-20 lipoproteins without any consideration of any other lipoprotein classes or blood pressure provided considerations are limited to age and sex matched individuals Further one could separately calculate a table for S_f20-100 lipoprotein level versus risk of clinical coronary heart disease and for S_f100-400 lipoprotein level versus risk of such disease Additionally similar risk calculations could readily be made for the diastolic blood pressure alone in a fashion exactly analogous to that outlined in detail for the S_f0-12 lipoproteins Proceeding in this manner one would have five separate measurements and five separate risk calculations concerning an individual A particular person might be

twice as high as the average in terms of risk of coronary heart disease because of his S_f0 12 lipoprotein level but might be four times as high as the average because of his S_f12 20 lipoprotein level etc Clearly having five separate risk values to consider without a method for weighing the relative importance of each of these separate risk estimates would be very unwieldy and difficult to handle in clinical practice Therefore it is necessary to weld the separate sources of risk information together into some composite measures which best express the overall relative risks of any two individuals with respect to the development of future clinical coronary heart disease This problem may be approached in two stages first to unify all the lipoprotein risk calculations namely to get together in one composite measure of risk that information that derives from S_f0 12 12 20 20 100 and 100-400 lipoprotein measurements and second to evaluate the risk separately arising from blood pressure values Finally it is essential to combine these two risk evaluations into a single composite risk estimate which takes into account all the available information

It is important to re emphasize here that the reason why all the four separate lipoprotein classes must be taken into account is that each class provides information independent of all the others with respect to coronary disease risk Each class of lipoproteins is involved in the progression of sub-clinical coronary heart disease and hence contributes to the risk of ultimate clinical coronary heart disease If knowledge of the level of one lipoprotein class provided the level of the others then measurement of any one of the lipoprotein classes would suffice for present purposes However it is well known that a person may be high in S_f0 12 lipoproteins but low in all the other three lipoprotein classes whereas some other person may be equally high in S_f0 12 lipoproteins and high in one or more of the other three classes The latter person carries a higher risk of future clinical coronary disease than does the former The human population is so constituted that practically any combination of S_f0 12 12 20 20 100 and 100-400 lipoproteins is possible and does occur Hence the best evaluation of a person with respect to the risk of future clinical coronary heart disease is to be obtained by a combination of the evaluation that derives from each of the four classes sep-

all having S_f0 12 lipoprotein levels of 500 mg/100ml The data in *Table IX indicate that the* relative risk of future coronary heart disease for members of the high group is 3 90 times that of the low group What this means is that if the 1000 individuals with low S_f0 12 lipoprotein values and the thousand individuals with the high S_f0 12 values were in apparent clinical health (which means that they are in the sub clinical phase of coronary heart disease) and if both groups were observed for a time period such as two years clinical coronary heart disease would develop in some members of both groups If out of the thousand individuals with the lowest S_f0 12 levels there developed 10 cases of clinical coronary heart disease then the relative risk table means that out of the group of 1000 individuals with the high S_f0 12 levels there would be 3 90 times ten or 39 cases of clinical coronary heart disease Obviously it is true that even for the group with high lipoprotein levels *most* individuals do not develop *clinical coronary heart disease in a short specified time interval* such as two years but this represents no erroneous diagnosis of the *risk* for such persons No false assessment of a person s chance of development of coronary heart disease is represented by this fact It is simply inherent in the nature of a risk calculation that many persons will escape the disease even though they are individually characterized by a very high risk of such disease compared with other persons

In an entirely analogous manner one could treat the *S_f12 20* lipoprotein measurement to calculate a coronary heart disease risk value that corresponds with each and every level of the S_f12 20 lipoproteins without any consideration of any other lipoprotein classes or blood pressure provided considerations are limited to age and sex matched individuals Further one could separately calculate a table for S_f20 100 lipoprotein level versus risk of clinical coronary heart disease and for S_f100 400 lipoprotein level versus risk of such disease Additionally similar risk calculations could readily be made for the diastolic blood pressure alone in a fashion exactly analogous to that outlined in detail for the S_f0 12 lipoproteins Proceeding in this manner one would have five separate measurements and five separate risk calculations concerning an individual A particular person might be

100 cases where the mean value of each lipoprotein class is not as stabilized as it would be with a much larger series of cases the precise value of the weighting factors is not stably evaluated It is to be anticipated that the weighting factor determined for each class might fluctuate if studied in one series versus another and might fluctuate some as additional cases are added to the overall series Because of this sensitivity of the weighting factor to the exact difference in mean value for any lipoprotein class in the coronary and non-coronary cases it was decided to reduce this sensitivity by combining the S_f12 20 plus S_f20 100 plus S_f100-400 lipoproteins into one composite band and to derive a weighting factor for this band relative to the S_f0 12 band of lipoproteins as a first step At some future time it will be desirable to have specific weighting factors for each of the lipoprotein sub-classes but for the present within the limits imposed by the size of the series of cases studied it has been decided not to attempt to determine the weighting factor for all the separate bands The application of the analysis of Fisher to coronary disease cases in men of the age range of 40 59 years had led to a weighting factor for the S_f12-400 band of lipoproteins of approximately 1 75 times that for the S_f0 12 lipoproteins[31] Therefore instead of combining the S_f0 12 lipoprotein measurement directly with the S_f12-400 lipoprotein measurement to obtain a *composite* value one should first multiply the number of milligrams per 100 ml of S_f12-400 lipoproteins by 1 75 before adding it to the number of milligrams per 100 ml of S_f0 12 lipoproteins In order to reduce the composite values obtained to a composite value of convenient dimensions all values are arbitrarily divided by ten (This is really equivalent to use of centigrams per 100 ml instead of milligrams per 100 ml) This composite value of the S_f0 12 lipoprotein level plus 1 75 times the S_f12-400 lipoprotein level had been designated as an *Atherogenic Index or A.I value*[31] This A I value *need imply nothing* with respect to arteriosclerosis or atherogenesis but simply is a composite value expressive of the weighted importance assigned to each of the lipoprotein classes with respect to coronary heart disease To be sure the name A I value or Atherogenic Index value was chosen because it was strongly surmised that it had to do with atherogenesis

arately If each lipoprotein class were exactly equal in importance with respect to the development of coronary heart disease that is if one milligram percent of S_f0 12 lipoproteins were equivalent in its effect to one milligram percent of S_f12 20, or one milligram percent of S_f20 100 or one milligram percent of S_f100-400 lipoproteins there would be a very simple procedure available for rating an individual Simple addition of the values for the S_f0 12 12 20, 20 100 and 100-400 lipoprotein levels to yield the S_f0-400 level could be performed Then in a manner similar to that described above for the S_f0 12 lipoproteins the risk of future coronary heart disease as related to the S_f0-400 level could be calculated This simplest approach of assuming that each milligram percent of every lipoprotein class means the same thing as each milligram percent of any other lipoprotein class would be certainly a step in the right direction for producing a composite risk estimate However there exist methods for treating this problem a little more critically instead of *assuming* that each milligram percent of a particular lipoprotein class is equivalent to one milligram percent of any other class with respect to coronary heart disease The British statistician Fisher[30], has developed a statistical method for dealing with problems such as this which allows calculation of a weighting factor to be applied to each of the measurements before adding the separate measurements For example, should Fisher s method indicate that S_f12 20 lipoproteins deserve a weighting factor of 2 compared with a weighting factor of 1 for S_f0 12 lipoproteins that S_f20 100 lipoproteins deserve a weighting factor of 2½ and that S_f100 400 lipoproteins a weighting factor of 3 then instead of adding together the milligrams percent directly one would add the milligrams percent of S_f0 12 plus 2 times the milligrams percent of S_f12 20 plus 2½ times the milligrams per cent of S_f20 100 plus 3 times the milligrams percent of S_f100-400 to obtain a composite value that best characterizes the individual The precise values of the weighting factors for each lipoprotein class are somewhat sensitive to the magnitude of the difference in average lipoprotein levels between coronary disease and non coronary disease cases for each of the lipoprotein classes There fore with a small series of cases of coronary disease even a series of

the S_f0 12 lipoproteins The Atherogenic Index value or A I value is calculated for each person from his lipoprotein levels This can be done for the base population of 10 000 (40-49 year old) men in apparent health as discussed previously and can be done for a series of coronary disease cases that would in time grow out of such a base population The persons in both the original healthy series and the clinical coronary disease series can be ranked in ten categories from the Atherogenic Index values for the lowest 10% of the healthy group up through the values for the highest 10% of the healthy group These values are categorized in Tables X and XI From these data the number of coronary disease cases per 1000 healthy persons in each Atherogenic Index category is immediately available The ratio of the number of coronary disease cases per thousand healthy men for any two Atherogenic Index categories is *directly* the relative risk of clinical coronary heart disease for these categories Such relative risks are presented in Table XII

The Atherogenic Index composite risk calculation takes into account all the information from the various lipoprotein measurements but does not take into account the blood pressure information The blood pressure will be considered below At the moment consideration must be given to the problem of how

TABLE X

Ranges of Atherogenic Index Values Each Comprising 1000 Men Out of a Base Population of 10 000 Overtly Healthy Men (Age 40-49 Years)

Atherogenic Index Categories Each Containing 1000 Men	*Range of Atherogenic Index Values*
Lowest category of 1000 men	Below 48
2nd category of 1000 men	49 55
3rd category of 1000 men	56-61
4th category of 1000 men	62-67
5th category of 1000 men	68 73
7th category of 1000 men	74 78
8th category of 1000 men	9 87
9th category of 1000 men	88 9[illegible]
Highest category of 1000 men	97 108
	Above 109

in the coronary arteries. However, since this entire thesis is being developed without any need to refer to atherogenesis, the A.I. value can *simply be defined* as the S_f 0-12 lipoprotein level plus 1.75 times the S_f 12-400 lipoprotein level. As an illustration of the calculation of Atherogenic Index values, the following example is considered. If a person shows 365 mg/100ml of S_f 0-12 lipoproteins and 150 mg/100ml of S_f 12-400 lipoproteins, the Atherogenic Index value will be equal to 365 plus 1.75 times the 150, all divided by ten, which yields an A.I. value of 63 units. Such a composite value is a step closer to the best composite value than that obtained by simply adding all the lipoprotein measurements together because it takes into account the weighted importance of the S_f 12-400 lipoproteins. It is to be anticipated that when a larger series of coronary disease cases is studied, and especially when a large series has arisen out of an original base population of individuals and the mean difference for each of the lipoprotein classes is fixed more precisely for the coronary disease cases versus the matched controls, the weighting factor of 1.75 for the S_f 12-400 lipoproteins versus 1.0 for the S_f 0-12 lipoproteins may change some. It may go down from 1.75 or it may go up some. However, none of the conclusions derived from utilization of the 1.75 value will be appreciably altered by such a shift in the value. The crucial issue to understand is that since a person derives his risk of future clinical coronary disease from all four classes of lipoproteins (S_f 0-12, S_f 12-20, S_f 20-100 and S_f 100-400) they must *all* be considered. For the present time the best weighting factor for S_f 12-400 lipoproteins appears to be approximately 1.75 times that for the S_f 0-12 lipoproteins, but the composite value derived thereby is not critically affected for clinical purposes should the weighting factor finally need minor revision upward or downward.

The availability of the composite Atherogenic Index value which takes *all* the lipoprotein information into account makes it possible to evaluate the risk of future clinical coronary heart disease with complete lipoprotein information for each case rather than with just the S_f 0-12 lipoprotein levels as was developed for illustrative purposes earlier in this chapter. The procedure for such risk evaluation is precisely that which was employed with

TABLE XII

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION FOR VARIOUS ATHEROGENIC INDEX VALUES (40-49 YEAR OLD MEN)

(Uncorrected for association of Diastolic Blood Pressure with Atherogenic Index Values)

Atherogenic Index (units)	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 30-34 units)*
30	1.00
35	1.06
40	1.13
45	1.20
50	1.33
55	1.60
60	2.13
65	2.66
70	3.40
75	4.53
80	6.20
85	8.06
90	10.1
95	12.7
100	15.6
105	19.0
110	23.2

THE RISK OF CORONARY HEART DISEASE ARISING FROM DIASTOLIC BLOOD PRESSURE

In the immediately preceding discussion the problem of calculating the risk of clinical coronary heart disease by measurement of the Atherogenic Index alone has been elaborated. These calculations are correct of and by themselves. If this were all that could be done with the prediction problem, it would represent a great step ahead of no knowledge at all. However in Chapter IV it was demonstrated that the blood pressure is a factor independent of the lipoprotein levels in determining the risk of clinical coronary heart disease. Therefore it should be possible to improve the segregation of individuals with respect to their risk of future clinical coronary heart disease by taking into

TABLE XI

DISTRIBUTION OF 113 MYOCARDIAL INFARCTION CASES INTO THOSE RANGES OF ATHEROGENIC INDEX VALUES WHICH SEGREGATE THE HEALTHY POPULATION INTO GROUPS EACH CONTAINING 10% OF TOTAL GROUP

Atherogenic Index Ranges for Each Category (Units)	*Number of Myocardial Infarction Cases in each Atherogenic Index Range*
48 and below	2
49 55	2
56 61	3
62 67	4
68 73	5
74 78	7
79 87	11
88 96	18
97 108	25
109 and above	36
Total Number of Cases	113

long in advance of occurrence of clinical coronary heart disease the prediction of relative risk based upon the Atherogenic Index is valid Precisely the same considerations hold for the Atherogenic Index as held for the lipoprotein measurements out of which it is derived since it is simply a composite measure expressing the information contained in the lipoprotein measurements In the previous discussion (Chapter III) it was shown that the lipoprotein elevation occurs in advance of clinical coronary heart disease by at least one to three years It was indicated further from the study of population trends and the study of individuals that persons with high lipoprotein values and hence high Atherogenic Index values remain high whereas those who are low remain low during most of adult life Therefore the period of one to three years of predictive value may in all likelihood be extended to 5 10 15 or even 20 years before the occurrence of clinical heart disease

values is directly a measure of *risk* of myocardial infarction for that particular blood pressure range These data then can be used to construct a table of risk in terms of the number of infarction cases per 1000 persons at risk at successive blood pressure values By setting this risk equal to 1 0 at some arbitrary diastolic pressure value e g 50 mm Hg the risks for all other blood pressure values can be expressed *relative* to the risk at 50 mm Hg This set of relative risks of myocardial infarction for various diastolic blood pressure values is presented in Table XIII Thus wholly independent of any of the lipoprotein information the relative risk of clinical coronary heart disease has been calculated for various diastolic blood pressure values If the lipoprotein levels were wholly unrelated to blood pressures the calculation of the risk due to elevation of blood pressure could be immediately superimposed upon the risk due to the blood lipoproteins However there is a weak correlation of Atherogenic Index values with blood pressure levels meaning that in the population at large as the Atherogenic Index rises there is anticipated a slight rise in average blood pressure levels and conversely as the diastolic blood pressure rises there is anticipated a slight rise in the average Atherogenic Index value Therefore a small part of the increased risk of clinical coronary heart disease at a particular elevated Atherogenic Index value is the result of the increased blood pressure which on the average is associated with that elevation in Atherogenic Index value Since this rise in blood pressure level with Atherogenic Index is known the table of risk versus Atherogenic Index can be corrected for the risk rise occasioned by the average rise in blood pressure which accompanies the rise in Atherogenic Index In Table XIV (a) is presented the risk versus Atherogenic Index data corrected for the association of blood pressure with Atherogenic Index

The rise in average Atherogenic Index value with rise in diastolic blood pressure value in the population at large is also significant especially at blood pressures above 70 mm Hg For diastolic blood pressures below 70 mm Hg there is almost no detectable change of average Atherogenic Index value with change in blood pressure Above 70 mm Hg there is approxi

account the blood pressure levels as well as the Atherogenic Index values. How is this to be done? In precisely the same fashion as was done for the Atherogenic Index, a population sample of 10,000 men can be divided into 10 sub-segments each containing 1000 men ranked upon diastolic blood pressure values. It is known from data such as those of Yater and co-workers what the distribution of diastolic blood pressure values would be for a group of myocardial infarction cases that would arise out of such a base population of 10,000 men. Therefore the number of myocardial infarction cases for each blood pressure range containing 1000 of the men of the original base population is available from the Yater data. The number of myocardial infarction cases per 1000 men for each range of diastolic blood pressure

TABLE XIII

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION AT VARIOUS DIASTOLIC BLOOD PRESSURE VALUES (MALES)

(Uncorrected for association of Atherogenic Index values with Diastolic Blood Pressure)

Diastolic Blood Pressure mm Hg	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 50 mm Hg)*
50	1.00
55	1.11
60	1.28
65	1.72
70	2.89
75	5.11
80	7.33
85	9.66
90	12.4
95	15.7
100	19.2
105	22
110	26.2
115	30.2
120	34.6
130	39.1
140	41.6
150	50.2

But since the relationship of Atherogenic Index with relative risk of myocardial infarction is available (Table XII) it is readily possible to correct the blood pressure risks for the rise in Atherogenic Index with rise in blood pressure. This is illustrated as follows. At a blood pressure of 50 mm Hg the average Atherogenic Index value for 30-39 year old men is 66.0 units, whereas for a blood pressure of 90 mm of Hg the average Atherogenic Index is 70.6 units. Such a rise in Atherogenic Index itself raises the risk of myocardial infarction. From Table XII this relative risk for 70.6 A.I. units is approximately 1.24 times that

TABLE XIV(b)

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION AT VARIOUS DIASTOLIC BLOOD PRESSURE VALUES (MALES)

(Corrected for association of Atherogenic Index values with Diastolic Blood Pressure)

Diastolic Blood Pressure mm Hg	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 50 mm Hg)*
50	1.00
55	1.0[illegible]
60	1.09
65	1.3[illegible]
0	2.01
7	3.23
80	4.16
85	4.98
90	5.79
95	6.69
100	7.53
105	8.06
110	8.[illegible]0
115	9.32
120	9.82
130	10.8
140	11.7
150	12.5

Each value in this table was obtained by correction of the risks of Table XII for the association of Atherogenic Index values with diastolic blood pressure utilizing the data of Table XII. A second correction which is essentially a complete correction was made by utilizing the first corrected value from Table XII.

mately a 2.4 unit rise in Atherogenic Index for a 10 mm Hg rise in diastolic pressure. When the relative risk of myocardial infarction versus diastolic pressure is estimated directly from blood pressure distributions for persons in health and for the myocardial infarction cases that grow out of a healthy population, *part* of the increased risk with increased blood pressure is really the result of the rise in Atherogenic Index with rise in pressure.

TABLE XIV (a)

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION FOR VARIOUS ATHEROGENIC INDEX VALUES (40-49 YEAR OLD MEN)

*(Corrected for Association of Diastolic Blood Pressure with Atherogenic Index Values)**

Atherogenic Index (units)	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 30 A.I. units)*
30	1.00
35	1.05
40	1.10
45	1.15
50	1.27
55	1.48
60	1.92
65	2.35
70	2.93
75	3.84
80	5.17
85	6.61
90	8.15
95	9.92
100	11.7
105	14.1
110	16.8
115	19.8
120	23.1
125	26.[illegible]
130	30.6

* Each value in this table was obtained by correction of the risks of Table XII for the association of diastolic blood pressure with Atherogenic Index value utilizing the data of Table XIII. A second correction which is essentially a complete correction was made utilizing the data in Table XIV (b).

from the blood pressure Such combination is readily possible if one approximation is made an approximation that is almost certain to be an excellent one This approximation is that if a particular elevation in Atherogenic Index value multiplies the coronary disease risk by a certain factor for persons all of whom have one particular blood pressure value it multiplies the risk by the same factor for persons all of whom have some other blood pressure value An illustration of this approximation follows Our previous calculations indicate that the risk of future coronary disease doubles for an increase in Atherogenic Index value from 50 units to 65 units in 40-49 year old men (see Table XII) The approximation being made is that this would hold true if two men were being compared both of whom had diastolic blood pressures of 70 mm Hg or if both of whom had some other diastolic pressure such as 80 mm 90 mm or 100 mm Hg The analogous approximation is made that if a particular elevation in diastolic blood pressure multiplies the coronary disease risk a certain amount for persons all of whom have one particular Atherogenic Index value it multiplies the risk by the same factor for persons all of whom have some other Atherogenic Index value If either of these approximations deviates from actuality at all it is extremely doubtful that any such deviation will be appreciable relative to the risk factors that will apply in the comparison of various persons

The combination of the future coronary heart disease risk from blood pressure measurement with that from Atherogenic Index values now becomes simplified Let us set the relative risk for the 45 year old man who is characterized by an Atherogenic Index value of 30 units and a diastolic blood pressure value of 50 mm Hg at 1 0 (On a *relative* scale the risk of a person can be arbitrarily set at 1 0 for some convenient set of Atherogenic Index and diastolic pressure values) Now if a 45 year old man whose Atherogenic Index is 85 units and whose diastolic blood pressure is 75 mm Hg is considered how does he rate compared with the first man with an Atherogenic Index of 30 units and a diastolic pressure of 50 mm Hg? From Table XIV (a) the corrected relative risk in passing from an Atherogenic Index value of 30 units to 85 units is 6 61 times as high Now since this is the

for 66.0 A.I. units. Therefore an excellent correction of the relative risk of myocardial infarction for a blood pressure of 90 mm. Hg versus that for a blood pressure of 50 mm. Hg is achieved by multiplying that relative risk by 1/1.24 or 0.81. When this is done the relative risk for the two pressures no longer has within it that increment in risk due to the Atherogenic Index elevation which goes with the blood pressure elevation. In Table XIII the relative risk for a blood pressure of 90 mm. Hg is listed as 12.4 times that for a blood pressure of 50 mm. Hg. Multiplying 12.4 by 0.81 yields 10.0, which is the relative risk for a blood pressure of 90 mm. Hg compared with that for 50 mm. Hg *after removal* of the increase in relative risk which results from the association of Atherogenic Index values with blood pressure levels. The relative risk of myocardial infarction for every diastolic blood pressure value can be corrected in an entirely analogous manner. In Table XIV (b) are presented the risk versus diastolic pressure values corrected for the effect of the association of rising average Atherogenic Index with rising blood pressure. Therefore these corrected risks of myocardial infarction for each blood pressure value are free of the effects of Atherogenic Index alteration. It is this corrected table of relative risks associated with various blood pressure values that must be used in all subsequent calculation of *overall* risk of myocardial infarction.

COMBINATION OF ESTIMATES OF RISK OF MYOCARDIAL INFARCTION TO OBTAIN OVERALL RISK

Medical interest centers about the *overall ranking* of apparently healthy individuals with respect to the chance or risk of development of future clinical coronary heart disease. Since risk rises with increasing Atherogenic Index values and independently with increasing diastolic blood pressure values, it is evident that the overall risk of a person with elevation *in both these* factors must be higher than that for a person with an equivalent elevation only in *one* of the two factors. It is essential therefore that some practical method be developed to combine the risks estimated separately from the Atherogenic Index value and

The *overall risk* is therefore 16 8x7 53 or 126 5 times that of a person with an Atherogenic Index of 30 units and a blood pressure of 50 mm Hg

Similarly, for Case (b)

From Atherogenic Index the relative risk is 1 10 times that for an Atherogenic Index of 30 units

From diastolic pressure the relative risk is 7 53 times that for a diastolic pressure of 50 mm Hg

The *overall risk* is 1 10x7 53 or 8 28 times that of a person with an Atherogenic Index of 30 units and a blood pressure of 50 mm Hg

For Case (c)

From Atherogenic Index the relative risk is 16 8 times that for an Atherogenic Index of 30 units

From diastolic pressure the relative risk is 1 09 times that for a diastolic pressure of 50 mm Hg

The *overall risk* is 16 8x1 09 or 18 3 times that for a person with an Atherogenic Index of 30 units and a blood pressure of 50 mm Hg

For Case (d)

From Atherogenic Index the relative risk is 1 10 times that for an Atherogenic Index of 30 units

From diastolic pressure the relative risk is 1 09 times that for a diastolic pressure of 50 mm Hg

The *overall risk* is 1 10x1 09 or 1 20 times that for a person with an Atherogenic Index of 30 units and a blood pressure of 50 mm Hg

With these calculated risks any two of these men can now be directly compared with respect to *overall risk* of coronary heart disease The man with the highest risk (Case (a)) has 126 5 times the risk of the person with an Atherogenic Index of 30 units and a diastolic pressure of 50 mm Hg The man with the lowest risk (Case (d)) has 1 20 times the risk of a person with an Atherogenic Index of 30 units and a diastolic pressure of 50 mm Hg The comparison of Case (a) and Case (d) is made by comparing 126 5 with 1 20 Therefore Case (a) has 126 5/1 20 or 105 1 times the coronary heart disease risk of Case

increase in risk for the Atherogenic Index change without change in blood pressure it is now appropriate to consider the risk rise for the blood pressure increase holding the Atherogenic Index constant In Table XIV (b) it is shown that a diastolic blood pressure rise from 50 mm Hg to 75 mm Hg corresponds to a relative risk of 3 23 times *The overall risk of coronary heart disease is obtained by multiplication of that arising from the Atherogenic Index by that arising from the blood pressure* Therefore multiplying 6 61x3 23 one obtains 21 4 Therefore the net or overall risk of this person is 21 4 times that of the person with an Atherogenic Index of 30 units and a blood pressure of 50 mm Hg Thus to compare the coronary disease risk of *any person of this age with that for any other person it is simply* necessary to multiply together the separate factors for increase or decrease in risk with the change of Atherogenic Index and the change in blood pressure respectively Since relative risk was set at 1 0 for an Atherogenic Index of 30 units and a blood pressure of 50 mm all persons should have their risks calculated with respect to these reference points and then after multiplying the Atherogenic Index risk by the blood pressure risk the overall risk thereby obtained may be compared directly for the individuals concerned This procedure is illustrated below with consideration of four types of cases

Case (a) A man 45 years of age with a high diastolic blood pressure (100 mm Hg) and a high Atherogenic Index value (110 units)

Case (b) A man 45 years of age with a high diastolic pressure (100 mm Hg) and a low Atherogenic Index value (40 units)

Case (c) A man 45 years of age with a low diastolic pressure (60 mm Hg) and a high Atherogenic Index (110 units)

Case (d) A man 45 years of age with a low diastolic pressure (60 mm Hg) and a low Atherogenic Index value (40 units)

For Case (a)

From Table XIV (a) the relative coronary disease risk (for Atherogenic Index) is 16 8 times that of a person with an Atherogenic Index of 30 units

From Table XIV (b) the relative coronary disease risk (for blood pressure alone) is 7 53 times that for a person with a diastolic pressure of 50 mm

cases with Case (d) they can be directly compared Thus Case (b) has 8.28/18.3 = 0.45 times the risk of Case (c) This last intercomparison illustrates how the effect of a high Atherogenic Index can be offset by the effect of a low diastolic blood pressure and vice versa *Overall risk* evaluation demands consideration of both Atherogenic Index and blood pressure

The illustrative examples above of calculation of overall risk of coronary heart disease were for the intercomparison of 40-49 year old men Similar calculations are of course of interest to the clinician for the intercomparison of 30 39 year old men with each other of 50 59 year old men with each other and of 60 69

TABLE XVI

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION FOR VARIOUS ATHEROGENIC INDEX VALUES (50 59 YEAR OLD MEN)

(Corrected for Association of Diastolic Blood Pressure with Atherogenic Index Values)

Atherogenic Index (units)	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 30 34 units)*
30	1.00
35	1.02
40	1.05
45	1.15
50	1.22
	1.39
60	1.58
65	1.99
70	2.59
75	3.25
80	4.17
85	5.02
90	5.91
95	6.81
100	[illegible]
105	8.81
110	10.0
115	11.2
120	12.8
125	14.3
130	16.0

(d) Thus it is seen is a relatively enormous segregation of these two cases upon coronary heart disease risk based upon the two measurements, Atherogenic Index and blood pressure Cases (b) and (c) have intermediary values of the *overall risk* Case (b) having a risk of 8 28/1 20 or 6 9 times that of Case (d) and Case (c) having a risk of 18 3/1 20 or 15 3 times that of Case (d) It is of course not necessary to compare all the other

TABLE XX

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION FOR VARIOUS ATHEROGENIC INDEX VALUES (30 39 YEAR OLD MEN)

(Corrected for association of diastolic blood pressure with Atherogenic Index Values)

Atherogenic Index (units)	*Relative Risk of Myocardial Infarction (setting risk = 1 00 at 30)*
30	1 00
35	1 24
40	1 46
45	1 68
50	1 90
55	2.20
60	2 59
65	3 10
70	3 78
75	4 97
80	6 46
85	8.20
90	10 2
95	12 0
100	13 8
105	16 0
110	18 8
115	22.2
120	26 3
125	30 4
130	35.3
135	40 1
140	45 0
145	50 6
150	55 6

cases with Case (d) they can be directly compared Thus Case (b) has 8.28/18.3 = 0.45 times the risk of Case (c) This last intercomparison illustrates how the effect of a high Atherogenic Index can be offset by the effect of a low diastolic blood pressure and vice versa *Overall risk* evaluation demands consideration of both Atherogenic Index and blood pressure

The illustrative examples above of calculation of overall risk of coronary heart disease were for the intercomparison of 40–49 year old men Similar calculations are of course of interest to the clinician for the intercomparison of 30–39 year old men with each other of 50–59 year old men with each other and of 60–69

TABLE XXI

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION FOR VARIOUS ATHEROGENIC INDEX VALUES (50–59 YEAR OLD MEN)

(Corrected for Association of Diastolic Blood Pressure with Atherogenic Index Values)

Atherogenic Index (units)	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 30–34 units)*
30	1.00
35	1.02
40	1.05
45	1.15
50	1.22
55	1.32
60	1.58
65	1.99
70	2.59
75	3.25
80	4.17
85	5.02
90	5.91
95	6.84
100	7.74
105	8.81
110	10.0
115	11.2
120	12.8
125	14.3
130	16.0

(d) This it is seen is a relatively enormous segregation of these two cases upon coronary heart disease risk based upon the two measurements Atherogenic Index and blood pressure. Cases (b) and (c) have intermediary values of the *overall risk*, Case (b) having a risk of 8.28/1.20 or 6.9 times that of Case (d) and Case (c) having a risk of 18.3/1.20 or 15.3 times that of Case (d). It is of course not necessary to compare all the other

TABLE XX

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION FOR VARIOUS ATHEROGENIC INDEX VALUES (30-39 YEAR OLD MEN)

(Corrected for association of diastolic blood pressure with Atherogenic Index Values)

Atherogenic Index (units)	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 30)*
30	1.00
35	1.24
40	1.46
45	1.68
50	1.90
55	2.20
60	2.59
65	3.10
70	3.78
75	4.97
80	6.46
85	8.20
90	10.2
95	12.0
100	13.8
105	16.0
110	18.8
115	22.2
120	26.3
125	30.4
130	35.3
135	40.1
140	45.0
145	50.6
150	55.6

genic Index data These tables are to be used for calculations of relative risk within each age decade just as in the illustrative examples above for 40-49 year old men

THE PROBLEM OF AGE IN THE PREDICTION OF FUTURE CLINICAL CORONARY HEART DISEASE

Since all the development of overall risk estimates of future coronary heart disease was carried through holding age bracket constant such risk estimates are appropriate to compare a particu lar man of one age e g 44 years with another man also 44 years of age Stretching the estimates one can without appreciable error compare two men in the same age decade e g 40-49 years even though they differ in age by a couple of years However it would *not* be appropriate to use such risk tables directly to compare a 35 year old man with a 65 year old man Nor would it be permissible to use these tables directly to compare a 40 year old woman with a 40 year old man since the tables were developed with data derived from measurements on men But every clinician wants to be able to make precisely such compari sons since he is interested in how two people rate in terms of risk of myocardial infarction whatever may be their age and whether or not both are of the same sex The problem of trans ferring the predictive tables to the female sex will be dealt with in extenso in Chapter VIII The problem of intercomparisons between men of widely separated ages is best handled by bring ing in evaluation of absolute risks of coronary heart disease in addition to relative risks

ABSOLUTE RISK OF CORONARY HEART DISEASE VERSUS RELATIVE RISK

Relative risk estimates for any two individuals describe whether one of them is two four ten or more times as likely to develop clinical coronary heart disease in a particular time interval as is the other As stated above such risks have been evaluated for the case where both individuals are of the same or nearly the same age However if the risk estimates were con verted to an *absolute* basis instead of the relative basis there

year old men with each other Since for each age decade under consideration a table of risk versus Atherogenic Index and risk versus diastolic blood pressure is needed such tables must be provided The table of risk versus diastolic blood pressure which is based upon the magnitude of the difference in blood pressure for Yater's series of cases of coronary heart disease will be used for all the age groups since no better data are available for each specific age group It is doubtful that there would be significant alterations in the relative risk due to blood pressure if separate tables were available for each age group However, specific data are available from which tables of risk versus Athero genic Index can be separately constructed for each additional age decade namely 30 39 years 50 59 years and 60 69 years Tables XV XVI, and XVII provide these relative risk versus Athero-

TABLE XVII

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION FOR VARIOUS ATHEROGENIC INDEX VALUES (60 69 YEAR OLD MEN)

(Corrected for Association of Diastolic Blood Pressure with Atherogenic Index Values)

Atherogenic Index (units)	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 30.41 units)*
30	1.00
35	1.02
40	1.05
45	1.15
50	1.41
55	1.74
60	2.34
65	3.19
70	4.31
75	5.42
80	6.50
85	7.70
90	8.95
95	10.2
100	11.4
105	13.0
110	14.6
115	16.5

fore for the 35 year man with average Atherogenic Index (70 2 units) and average blood pressure (71 0 mm Hg) as it is for the hypothetical reference man with Atherogenic Index of 30 units and diastolic pressure of 50 mm Hg Now since the absolute risk or incidence rate of fatal coronary disease is 50 per 100 000 per year for the average man it must be 50 divided by 8 53 or 5 86 per 100 000 per year for the hypothetical reference man at 30 units of Atherogenic Index and 50 mm Hg Since all of our relative risk calculations described previously are made in terms of the risk compared with the hypothetical reference man it becomes immediately possible to convert any relative risk calculated into the absolute risk by simply multiplying by the value 5 86 per 100 000 per year This may be illustrated as follows Suppose a 35 year old man has an Atherogenic Index of 100 units and a diastolic pressure of 90 mm Hg From Table XV from Atherogenic Index his risk relative to the hypothetical reference man (A I = 30 units) is 13 8 times as high From Table XIV from diastolic pressure his risk relative to the reference man (BP = 50 mm Hg) is 5 79 times as high Multiplying these values together we obtain 13 8x5 79 or 79 9 times as high for the overall relative risk The conversion to absolute risk is achieved by multiplication of 79 9 by 5 86 This yields an absolute risk of 468 per 100 000 per year for the 35 year old man with an Atherogenic Index of 100 units and a blood pressure of 90 mm Hg This value of absolute risk is directly comparable with similarly calculated absolute risks for men *at any age* *It is* therefore evident that having the absolute risk for the hypothetical reference man (A I = 30 units BP = 50 mm Hg) at each age is highly useful for the purpose of converting relative risks into absolute risks It was demonstrated above how this absolute risk is obtained for the hypothetical reference man of 35 years of age using the combination of the relative risk tables plus the U S Vital Statistics to provide the risk for the person with average Atherogenic Index and average blood pressure Such absolute risks for the hypothetical reference man for each decade have been calculated and are reproduced as follows

would exist no problem whatever to compare the risk for a 35 year old man with that for a 65 year old man or a man of any age *Absolute* risks are expressed in terms of the number of men developing clinical coronary heart disease per 100 000 persons exposed in a specific time period e g one year *Thus if a certain* 35 year old man belongs to a group where 10 out of 100 000 will develop clinical coronary heart disease in one year and a certain 65 year old man belongs to a group where 50 out of 100 000 will develop clinical coronary heart disease in one year it is obviously possible to compare these *absolute* risks *directly* and to state that this 65 year old man has five times the risk of clinical coronary heart disease as the particular 35 year old man under consideration *How are such absolute risks to be obtained for any two men?*

The U S Vital Statistics provide the average incidence rate of fatal coronary heart disease for men at various ages (see Chapter VII) Let us consider the use of such information to translate relative risks into absolute risks for any particular individual For 35 year old men in the United States the incidence rate of fatal coronary disease is approximately 50 per 100 000 persons per year This may be expressed otherwise as the *average risk* of fatal coronary heart disease for 35 year old men To a first approximation (and one completely adequate for all our purposes here) this risk may be considered to be that which applies to the 35 year old man *who has the average values of the Atherogenic Index and of the diastolic blood pressure*

For this age average Atherogenic Index=70 2 units and average diastolic blood pressure=71 0 mm Hg The question to ask now is What is the absolute risk for the hypothetical *reference* man of 35 years of age with an Atherogenic Index of 30 units and a diastolic pressure of 50 mm Hg? The first step is to compare this hypothetical reference individual with the average man of 35 years of age From Table XV the relative risk of coronary disease for an Atherogenic Index of 70 2 units is 3 79 times that for an Atherogenic Index of 30 units From Table XIV the relative risk for a diastolic blood pressure of 71 0 mm Hg is 2 25 times that for a diastolic pressure of 50 mm Hg The *overall* relative risk for 3 79×2 25 or 8 53 times as high there

THE QUESTION OF "FALSE POSITIVE" PREDICTIONS

It is worthwhile contemplating the absolute risk values in connection with the question of so-called false positive prediction Thus for the illustration above for a 65 year old man with a high Atherogenic Index (100 units) and a blood pressure well above average namely 90 mm Hg the absolute risk of fatal coronary disease was calculated to be 8217 per 100 000 persons per year Out of 100 000 such men 8217 would die in one year of coronary heart disease *but* 91 783 would survive in that year Evidently many more people would survive the year than would die of coronary disease There are those who would ask the question Does this not mean that the Atherogenic Index blood pressure risk calculation has falsely indicated a high risk of fatal coronary heart disease? The answer is unequivocally and emphatically No Even though more persons will survive the year than will die 8217 deaths per 100 000 is still a very high risk and is in no sense a false prediction The entire point of such risk estimates is the development of an ability to select out of an otherwise homogeneous population sample those persons who carry 2 5 10 20 100 or 500 times the risk of coronary heart disease death than characterizes other members of the population sample The issue is *not* selection of some group of *persons all* of whom or *most* of whom will be dead of coronary disease within any specified short time interval It can readily be shown that the argument concerning false positives readily reduces to a logical absurdity Suppose *that a* risk category were identified where 995 out of 1000 persons would be dead of coronary disease in a one year period In this event those who talk of false positives might say that this is good prediction for a one year period but they could ask about the validity of the risk estimate for the five minute period just after the blood pressure was determined and the blood sample was withdrawn from Atherogenic Index determination Even for a group of persons in which 995 out of 1000 *will be dead* in one year it is true that more than 999 out of 1000 would still be alive after five minutes Does this mean that this group has been *falsely* predicted to show a high risk of coronary disease? Manifestly this type of reasoning concerning false positives *can* lead to ridiculous conclusions and

Age Decade	*Absolute Risk of Fatal Coronary Disease for the Hypothetical Reference Man at Atherogenic Index = 30 Units and Diastolic Pressure = 50 mm Hg*
30 39 years	5 86 per 100 000 per year
40-49 years	12 9 per 100 000 per year
50 59 years	56 1 per 100 000 per year
60 69 years	124 5 per 100 000 per year

Illustration of how these absolute risks allow direct comparison of men differing widely in age is now in order In the development above it was shown that a 35 year old man whose Atherogenic Index is 100 units and whose diastolic pressure is 90 mm Hg is 468 per 100 000 per year How would this compare with the risk of a 65 year old man having the same Atherogenic Index (100 units) and the same diastolic pressure (90 mm Hg)?

For a 65 year old man from Table XVII the relative risk for an Atherogenic Index of 100 units is 11 4 times as high as for the reference man with an Atherogenic Index of 30 units From Table XIV the relative risk for a diastolic blood pressure of 90 mm Hg is 5 79 times as high as for the reference man with a diastolic pressure of 50 mm Hg The overall *relative* risk for the 65 year old man with an Atherogenic Index of 100 units and a diastolic pressure of 90 mm Hg is therefore 11 4x5 79 or 66 0 times as high as for the hypothetical reference man of 65 years of age with an Atherogenic Index of 30 units and a diastolic blood pressure of 50 mm Hg But this hypothetical reference man has an *absolute* risk of fatal coronary heart disease of 124 5 per 100 000 per year Therefore the 65 year old man with an Atherogenic Index of 100 units and a diastolic pressure of 90 mm Hg has an absolute risk of 66 0x124 5 or 8217 per 100 000 per year The comparison of this 65 year old man with the 35 year old man having the *same* Atherogenic Index and the same blood pressure is made by dividing 8217 by 468 Therefore the 65 year old man has 17 6 times as high a risk of coronary heart disease as does a 35 year old man even though both have the same Atherogenic Index and the same blood pressure The procedure for comparing any two other men at any ages Atherogenic Indices and blood pressures would be identical to that just developed

THE INFLUENCE OF VARIABILITY OF THE ATHEROGENIC INDEX AND BLOOD PRESSURE MEASUREMENTS ON PREDICTIVE POWER

It is of course true that with respect to any biochemical measurement such as Atherogenic Index value or any physiological measurement such as blood pressure there is a certain degree of fluctuation observed if the measurement is made repeatedly on the same person This fluctuation in measurement originates from at least two major sources The first is what may be regarded as *biological* variation namely the fact that a human does not show absolutely constant values of very many biochemical or physiologic variables over a period of time The second major source of variation is that due to technical error of measurement What we see in the overall when a given variable is measured such as the Atherogenic Index or the blood pressure is the combined effect of biological variation and technical error in measurement As a result of the operation of these two factors a person will not show exactly the same Atherogenic Index value or blood pressure value determined on two separate occasions either a day week month or year apart It is true that such variation would tend to move the position of a person somewhat on a scale of risk of future coronary disease This hardly need interfere with the enormous usefulness of the predictive measurement First of all variation of the Atherogenic Index is in general small although it definitely exists Hence a person who is in the *highest quarter* of the population will in the main remain in the highest quarter of the population whereas a person in the lowest quarter of the population with respect to the Atherogenic Index will in the main remain in the lowest quarter The precise extent to which Atherogenic Index measurements vary for individuals over a period of one to three years is now known Studies are available for 213 consecutive men between the ages of 20 and 59 years of age upon whom Atherogenic Index measurements were made on one periodic employment examination and on a second examination one to three years later (Exclusion of the effect of major dietary alterations was achieved by elimination from this series of any men who had gained or lost five or more pounds in weight over the time inter

away from any constructive approach to the coronary heart disease problem

It is always pertinent when confronted with such problems to review the nature of the objectives toward which one is working In the prediction of risk of future clinical coronary heart disease the objective is *utilization* of the information obtained to take constructive steps toward *prevention* of that disease It would be remarkable indeed if there were a method available to determine that a particular individual is *the* one who will have a myocardial infarction in 30 days If this were possible every effort could be made to apply preventive measures for this particular individual Such prediction is simply not possible now nor does *it appear that it will be possible in the near future But* the methods described in this chapter do permit identifying individuals with five ten or more times the risk of development of clinical coronary heart disease in comparison with average individuals Can such information be utilized to achieve our objective? Let us suppose that a particular individual has been demonstrated to show *twice* the average risk of development of coronary heart disease during a one year period Suppose further that such risk can be reduced in half by medical measures If every person whose risk is twice or more than twice average had his or her risk cut in half by medical measures the net result of such a program would be a lowering of mortality due to coronary heart disease approximately by a factor of two This would obviously be considered as a major medical triumph The type of risk estimates developed here allow for progress toward precisely such a goal Great progress can definitely be made in this direction even though it is not possible to predict the date and hour that a specific individual will experience myocardial infarction or even to predict that he *ever* will While this approach will lead to advice of prophylactic measures for *some* persons who *might* escape the disease even with a high risk it would be utter folly to underestimate the real potential and power of this type of preventive medical approach to coronary heart disease

WHO IS IN NEED OF PREDICTION OF THE RISK OF FUTURE MYOCARDIAL INFARCTION?

From the data and calculations presented up to this point it is clear that a population of individuals otherwise comparable can be divided on the basis of lipoprotein and blood pressure measurement into groups characterized by a very low risk of coronary heart disease in a specified time interval an intermediary risk in the same time interval or a very high risk in the same time interval The question facing the clinician is What group of individuals is in need of such predictive information concerning the risk of future coronary heart disease? Certainly those who have already manifested clinical signs and symptoms of overt coronary heart disease are hardly in need of prediction of whether they are prone to develop coronary heart disease In the population at large no one has ever been able to distinguish by standard medical examinations including electrocardiography any group of adults who can be said to be free of the risk of future clinical coronary heart disease The suddenness of occurrence of clinical coronary heart disease in persons in the best of health eloquently refutes the possibility of pre selecting by usual means any part of the population which carries an excessive risk from any part of the population which has little or no risk This being the case it is quite clear that *every adult* in the population represents without auxiliary special information a potential candidate for future clinical coronary heart disease Therefore every adult in the population is a candidate for *evaluation* of his risk of future coronary heart disease To be sure we know from vital statistics for the country that men of 25 years of age have a lesser risk of coronary heart disease than men of 35 years of age and correspondingly men of 35 years of age have a lesser risk than do men of 45 years of age etc With respect to imminence of disease it might be considerably more pertinent to segregate 45 year old men on the basis of risk of future clinical coronary heart disease than to do so for 25 year old men However another consideration must temper this view All the evidence indicates that the clinical aspects of coronary heart disease represent a culmination of the slow accumulation of coronary artery narrowing The major predictors of future clinical coronary disease

val between the two examinations) The best approximation of the true Atherogenic Index values for these cases is to take the average of the two measurements for each person When this is done it is found that the following holds

(a) 58% of these men varied fewer than 5 Atherogenic Index units from their average value over the 1 3 year period

(b) 25% of these men varied between 5 and 10 units from their average value over the 1 3 year period

(c) 13% of these men varied between 10 and 15 units from their average Atherogenic Index value over the 1 3 year period

(d) Only 4% of these men varied 15 or more units from their average Atherogenic Index value over the 1 3 year period

Therefore it is relatively rare for a man to be significantly misclassified on the Atherogenic Index—coronary disease risk scale even with a *single* measurement of the Atherogenic Index value Multiple measurements over a period of time for an individual will allow placement on the risk scale with great precision

The blood pressure measurement is somewhat more variable both on a biological and technical basis However here again if one is interested in assessing the risk of someone with respect to coronary heart disease (and such risk is probably one of the most important measurements that can be made for an individual in health in the effort to safeguard his future health) one can certainly afford to make repeated blood pressure measurements Since the blood pressure does tend to vary some one might want to make a series of measurements spaced at specific time intervals to determine the individual s usual or habitual blood pressure Blood pressure measurements taken under relatively standardized conditions should be utilized in coronary disease risk estimates Thus if an individual happened to have a single blood pressure value of 100 mm Hg under a single special circumstance whereas most of the time he is at 80 millimeters of mercury it would hardly make sense to consider 100 mm Hg as the pressure value to use in assessing coronary disease risk

measure with recent poliomyelitis immunization of adults and at least for military personnel and travelers innoculation for several other diseases However the idea that vascular disease may enter this realm of preventive medicine is one which will meet with some skepticism and lack of understanding in certain quarters Yet all the evidence points in this direction There will undoubtedly be those who say the idea of considering every adult as a patient or a potential patient with respect to a disease like coronary heart disease would mean a fabulous task for the medical profession It will be a fabulous task for the medical profession but one abundantly justified by the fabulous importance of the problem that lies before it in this field Further there will be some who will ask whether we might not dispense with individualization in prediction of heart disease risk through identification of those with lipoprotein metabolic errors and/or blood pressure elevation and instead develop a preventive hygiene that can be advised for the population at large broadly without the necessity for individual attention Preventive hygiene measures on a broad basis are highly desirable where feasible For example if it were discovered that a particular atmospheric pollutant resulting from industrialization of our cities were the cause of a particular disease certainly the best measure for minimization of the hazard due to this pollutant would be a concerted attempt to rid the atmosphere of it This would represent broad scale application of a generalized hygiene Similarly if it could be shown that a specific dietary element were injurious to a large number of individuals or to all one could recommend a generalized hygiene to eliminate this particular noxious agent from the dietary environment There is every reason to make progress in this direction of generalizing our efforts toward a preventive hygiene for coronary heart disease However as the evidence develops in this area it appears more and more that *individualization* will be needed and needed *over and above any such generalized measures* Thus it is now known that in certain individuals the S_f0 20 lipoprotein elevation is the primary reason for an increased risk of future clinical coronary heart disease In other individuals the S_f20-400 lipoprotein elevation is the primary reason for an increased risk of future coronary heart dis

namely the lipoprotein levels and the blood pressure appear to derive their relationship with clinical coronary heart disease via their relationship with coronary arteriosclerotic narrowing Therefore if a preventive regimen is to be devised for persons with high risks the prediction of risk should be accomplished as early as feasible in order to inhibit the slowly developing coronary artery narrowing and the corresponding accumulation of risk of ultimate clinical coronary heart disease This means that the earlier it is possible to use predictive information the more favorable the outlook for accomplishments in minimization of the risk of ultimate development of overt coronary heart disease By the time a man is in his twenties his lipoprotein levels can certainly provide a great deal of information concerning the risk of later clinical coronary heart disease This is the appropriate time to start evaluation of risk Further since there is no way of excluding *anyone* in the population as a potential bearer of a high risk of future coronary heart disease the need for screening the future risk of coronary heart disease extends over the entire population of adults of any country This is undoubtedly a rather radical concept to some However some reflection on the problem will readily reveal that unless and until this concept is understood and utilized broadly by the medical profession the real hope of inhibiting coronary heart disease and cutting down its enormous morbidity and mortality can hardly be realized This means an entirely new concept for the physician interested in vascular disease as to who is a patient We have in adult medicine for so long been oriented toward the therapeutic side of medicine treating diseases once they have become clinically manifest that it will undoubtedly be difficult both from the point of view of the physician and of the potential patient to alter this concept Yet the concept of preventive medicine has taken hold and is taking hold in new areas every day In pediatric practice for example the idea of minimizing the risk of such entities as pertussis typhoid fever tetanus diphtheria poliomyelitis and other diseases is well established and immunization of most children is routine Every child is regarded as a potential candidate for these diseases and hence is deserving of preventive medicine In the adult field this has been extended to some

many industries have for several years been in the habit of having annual preventive medical check ups Such preventive medical check ups are gradually coming to include additional features of examination laboratory and clinical which may discover predisposition to certain diseases at a time when preventive efforts may be really effective This concept of preventive hygiene is not new but simply one that requires extremely broad expansion to include thousands of times the numbers of individuals who are now covered by it But progress of this sort considering the educational aspects involved may take many years to achieve It would be naive to believe that simply stating the problem to the physician population and through that group to the public at large would see overnight the accomplishment of the desired end It is very important to attempt to lower the time gap between *application* of what we have available to us in our armamentarium of prevention of disease and its actual use to as few years as possible During such an interim time period a great deal can be accomplished by broadening the use of predictive methods for determining the risk of coronary disease to include at least those people who carry the most excessive risk of early coronary heart disease

As an illustration of this approach some glaring examples of such groups with very high potential coronary disease risk deserve consideration There exist perhaps as many as one percent of the individuals in the population of the United States who come from families characterized by a marked heritable tendency to have abnormally high levels of lipoproteins of one class or another In such families overt xanthomata are common xanthoma tuberosum xanthoma planum of the hands xanthoma tendinosum or xanthelasmata about the eyelids In these families not all individuals are afflicted with the abnormally high lipoprotein levels but many are Unless the members of such families are already characterized by manifest xanthomatosis they go unrecognized and nothing is done for them Some with overt xanthomatosis who have not yet developed overt cardiovascular disease are discovered by physicians because the patients are concerned over the cosmetic aspects of their lesions Indeed a fair number of such patients are discovered by dermatologists and cosmetic atten

ease In this latter group the S_f0-20 lipoproteins may be moderate or even very low in level In still other individuals it is an elevation of all the lipoprotein classes in this general region from S_f0-400 that accounts for the risk of future coronary heart disease And added to each of these possibilities there is the factor of elevation of blood pressure together with one or another type of lipoprotein elevation that creates a high risk of future coronary heart disease The metabolic factors which control the level of the S_f0-20 lipoproteins are not in general the same as those that control the level of the S_f20-400 lipoproteins This is already evident from the fact that individuals can be high in one class of lipoproteins but low in another It appears highly unlikely that the future will readily see a dietary approach or a pharmaceutical approach that will at once correct *all* the different types of metabolic aberrations that lead to lipoprotein elevation Therefore individualized attention appears inevitable Indeed a regimen that might favorably affect one lipoprotein class can be very unfavorable for another class Were sights focussed on the correction of just one of the lipoprotein classes involved without proper attention to the others in a mass generalization of a dietary or pharmacologic preventive hygiene a great deal of harm might accrue to certain individuals Such a result could hardly be called an aim of preventive medicine or of medicine in general Thus the existence of several types of defects that can lead to an increased risk of clinical coronary heart disease and the unlikely prospect that any simple specific preventive measure will work for everyone on a blind basis means that individualization of preventive medical efforts appears essential The facilities for measurement of the *status* of every adult individual with respect to lipoprotein level on a schedule such as every one to three years beyond the age of 25 years have long been available The problem will first be largely one of having the physician population recognize the need for such a preventive approach to the problem of coronary heart disease The public will then need to be educated by the physician concerning the vital role of *preventive* medicine with respect to coronary heart disease Already many individuals under the advice of their own competent physicians and the executives of

excessive rates Such persons are therefore in need of preventive measures to avert the same type of clinical occurrence as that experienced by the index case Certainly for anyone with overt coronary heart disease below the age of 40 years a lipoprotein analysis in all blood relatives is urgent With less force the same would hold true for the families of persons developing overt coronary heart disease between 40 and 50 years of age Another stigma that is common in the population and which is at times associated with a *lipoprotein disorder* on a heredo familial basis is arcus senilis The presence of a well marked arcus senilis in a relatively young person for example under 40 years of age distinctly suggests the individual deserves an early lipoprotein analysis A surprisingly high frequency of elevation of the S_f0 12 or S_f0 20 lipoproteins will be found in such cases

Diabetes mellitus will be considered in extenso in Chapter XII However at this time it can be emphasized that what excessive risk of coronary heart disease does exist for persons with diabetes mellitus arises largely if not completely from elevation of lipoprotein levels or elevation of blood pressure or both The lipoprotein and blood pressure status of every diabetic patient deserves early determination both from the prognostic and management aspects of that person s disease There is no longer any reason for the blanket generalization to the diabetic patient that he carries a hazard of premature coronary heart disease simply because he is diabetic Such risk can now be determined precisely If the particular diabetic patient should be one of the many fortunate diabetics who do not show the elevation in lipoproteins or the elevation in blood pressure which would accompany an excessive risk of coronary heart disease he could be vigorously re assured concerning his outlook by his medical advisor Thus even though there may be a period of time before the population at large is evaluated with respect to lipoprotein and blood pressure status every diabetic deserves an early evaluation Still another group that deserves consideration comprises those individuals who at one time or another have been treated for thyroid disease A large majority of these may have been treated for a previous hyperthyroidism and some for goiter without hyperthyroidism Many of these individuals are

tion is the major feature of therapy Yet it is well known that the individuals in such families who are characterized by extremely high lipoprotein levels are prime candidates for very early coronary heart disease and for other related entities such as peripheral vascular disease and cerebral vascular disease The rate at which the ranks of such families are decreased by premature deaths from coronary heart disease and its related entities is truly appalling with a large proportion of deaths occurring below forty years of age For those persons who manifest xanthomatosis there is not a great deal of difficulty in clinical diagnosis of the existence of the xanthomatosis but all too often nothing is clinically done for the members of these families without the overt lesions For example in a family where any individual has xanthoma tendinosum with its attendant massive S_f 0 12 or S_f 0 20 lipoprotein elevation there exists the high likelihood that brothers sisters other relatives and offspring even below the age of 5 years may already have the same massive lipoprotein defect as the index case These individuals not yet having developed skin lesions or tendon lesions are unaware of the tremendous hazard of coronary heart disease they may have inherited and nothing is generally done to attempt to reduce this hazard In such families *every* blood relative of individuals known to be characterized by xanthomatosis of any form requires urgent evaluation of the lipoprotein status as a first step toward broader application of the principle of preventive medicine in coronary heart disease

Other familial situations would deserve early consideration of an evaluation of the lipoprotein and blood pressure status for members of the family It is the rule to find that young individuals who develop clinical coronary heart disease show *extremely* elevated lipoprotein levels with this elevation frequently being heredo familial in origin Siblings of such individuals parents and children may well be found to be afflicted with a similar lipoprotein disorder Hence when coronary disease occurs at an early age in a person it is very pertinent to examine the lipoprotein status of every blood relative who is available in the effort to discover other members of the family in whom the coronary heart disease risk may be building up at

Chapter VI

THE FAMILIAL ASPECTS OF CORONARY HEART DISEASE

ONE OF the most widespread impressions in medicine concerning coronary heart disease is that it occurs prematurely in certain families Some cardiologists have crystallized this impression with statements to the effect that perhaps one of the best ways to avoid clinical coronary heart disease is to choose one s ancestors wisely The widespread character of this concept implies that there must be some evidence to support it and indeed there does exist a certain amount of evidence However it can be stated at the outset that the relationship between familial factors and coronary heart disease is far from a perfect one Therefore any broad *generalization* based upon a statement that a family history of longevity can be relied upon to protect against coronary heart disease or that a very poor family history insures that coronary disease will occur in a given individual will be very far from the truth

The real question of interest is whether or not familial factors operate in coronary heart disease in the population at large out of which is drawn the vast bulk of our patients with early clinical coronary heart disease In certain special types of families the hereditary or heredo familial aspect of clinical coronary heart disease is unquestioned since a very solid body of evidence has implicated a familial factor in these special groups predisposing to the occurrence of coronary disease This is true of those families in which a hyperlipoproteinemia of some variety is present Earlier such families had been described in terms of elevation of the serum cholesterol level or the blood total lipid level but now such entities can be more precisely defined and delineated in terms of the particular spectrum of lipoproteins

followed for a short period of time in the medical center or in the office in which they were originally diagnosed and treated Thyroid replacement therapy has been provided for many such patients who were left with a mild residual hypothroidism Yet it is very common for the individual himself to assume that such replacement therapy is temporary and eventually he may stop taking thyroid substance and may remain for years in a hypothyroid state Such individuals may not feel seriously ill or have sufficient special complaints referable to their thyroid status to seek medical care If they have been affected by thyroid deficiency to the extent that they acquire the marked elevation of S_f0 20 lipoproteins which characterizes thyroid deficiency (see Chapter XIII) they may be carrying a markedly excessive risk of future clinical coronary heart disease Therefore any individual who has for whatever reason at one time had a thyroidectomy or a treatment of thyroid disease by destructive agents such as x ray or radioactive iodine certainly deserves a periodic evaluation of the lipoprotein status to determine whether there is any need for replacement therapy with thyroid substance or one of its congeners

As one considers the several possibilities familial lipoprotein derangements thyroid disorders diabetes mellitus families of individuals with early coronary disease and others it becomes apparent that the groups in need of early evaluation of their status with respect to risk of coronary disease constitute large numbers of persons These groups certainly represent the basis for a minimum effort that the medical profession should make in a start toward a significant preventive medicine with respect to coronary heart disease Ultimately this effort must extend to everyone in the population at large

elevation Xanthoma tuberosum is common in these families Coronary heart disease at an early age is also rampant in this particular heredo familial disorder Again there appears to exist no evidence that at the same degree of elevation of lipoprotein level there would be any difference in the prognosis with respect to early coronary heart disease in the presence or absence of xanthomatosis A third group of individuals showing a heredo familial disorder of lipoprotein levels is that known as the essential hyperlipemia group This group of individuals is characterized in general by the absence of xanthomatous lesions These families are discovered when a member of the family is incidentally found to show markedly creamy serum in the fasting state They are characterized by massive elevation in lipoproteins from s_f20 to s_f100 and in most cases additional massive elevation of lipoprotein levels of those from s_f100 all the way to chylomicrons It is the presence of the very large lipoproteins in high concentration that accounts wholly for the extreme turbidity of the serum in such cases Characteristically the s_f0 12 lipoprotein levels are low in such cases and the s_f12 20 lipoprotein levels are usually not different from those in the population at large For some reason there is an erroneous concept in the literature that such individuals seem to be free of the risk of coronary heart disease This concept is distinctly incorrect for when such persons have the elevation of s_f20-400 lipoproteins they carry the high risk of coronary heart disease associated with such an elevation Most likely the reason for the good prognosis previously assigned to these individuals is that the handful of cases reported in the literature have in the main been children and very young adults As a result these individuals have been thought to be free of coronary disease risk in spite of their lipoprotein elevation when actually the reason why they are free of coronary heart disease is that they have been studied at such a relatively early age

Even if all these various heredo familial lipoprotein disorders are combined they may still be regarded as a rather special group when compared with the population at large Indeed such groups are considered so special that some workers refer to their disease of the vascular system as xanthomatosis of the vascular

which is abnormal[32] Families do exist with extreme elevation of one or another lipoprotein class and in these families it is well documented by evidence reported throughout the world that premature clinical coronary heart disease is rampant To be sure *some* of the members of these families escape premature clinical coronary heart disease but that there is a marked increase in the frequency of such disease in these families cannot be doubted One such type of family is that characterized by massive elevation of the s_f0 12 or s_f0 20 lipoprotein class In members of these families where the lipoprotein elevation is extreme and where enough time has elapsed xanthomatosis in the form of xanthelasma (xanthoma of the eyelids) xanthoma tendinosum and even planar xanthomatosis of the palms is observed There has been some debate in the literature concerning whether or not those members of the family who show the elevation in the blood lipids without the overt xanthomatosis really carry any pre disposition to coronary heart disease[33] There is very little question but that the real essence of this problem is that in order to develop xanthomatosis the level of lipoproteins has to be quite high and this lipoprotein elevation has to have existed for some period of time The absence of xanthomatosis in the presence of a high lipoprotein level is quite often traceable to the fact that the individual is relatively young[34] Given enough time many of these individuals do develop the xanthomatosis There exists no reason to expect that the lipoprotein elevation without xanthomatosis carries any different prognosis with respect to early coronary heart disease than does the same degree of lipoprotein elevation with the xanthomatosis provided of course that any age differential that exists is taken into account A second type of disorder which is a familial one is that characterized by massive elevation primarily in the S_f12 400 class of lipoproteins especially the S_f20 400 part of this class of lipoproteins In such families the lipoprotein derangement is also an inheritable trait with those members of the family who do inherit it showing the same lipoprotein disorder namely elevation of the s_f12 400 or s_f20 400 lipoprotein class It is interesting that on the average such individuals show a depression of the s_f0 12 lipoprotein level rather than an

directions The specific evidence available from such studies deserves critical examination here

DIRECT STUDIES OF THE INCIDENCE OF CARDIOVASCULAR DISEASE IN THE FAMILIES OF INDIVIDUALS WITH OVERT CORONARY HEART DISEASE

One study of the familial patterns in patients with coronary heart disease is that of Gertler and White[36] a part of their overall study of ninety seven men who had developed clinical coronary heart disease below the age of 40 years In that study there were 97 men who had developed coronary heart disease below the age of 40 years and 97 matched controls matched as well as possible by age sex and by other variables such as occupation The matched group of controls was overtly healthy and free of any symptoms or signs of clinical coronary heart disease Interviews conducted in the course of the examination of all these subjects developed data concerning the incidence of cardiovascular disease and deaths due to cardiovascular disease in the mothers in the fathers and in the siblings of the 97 men with clinical coronary heart disease and in the relatives of the group of matched controls It was found by Gertler and White that a significantly higher percentage of the fathers of men with coronary heart disease below 40 years had had cardiovascular disease or had died of cardiovascular disease than of the fathers of the matched control group The trend was in the same direction for the mothers of the men with coronary disease below the age of 40 years as compared with the mothers of the men in the matched control group although the total number of cases of cardiovascular disease among the mothers was too small to be statistically significant Similarly it was found that the brothers of the men with coronary heart disease below 40 years showed a higher reported incidence of cardiovascular disease than did brothers of the men in the matched control group The general conclusion that would be drawn from the study of the Gertler and White material is that cardiovascular disease is significantly more frequent in the families of men who suffer coronary disease below the age of 40 years than in men of the same age group free of overt coronary heart disease Unfortunately one major failing

system rather than arteriosclerosis of the vascular system There does not exist a valid justification for differentiation of the vascular lesions in the individuals in xanthomatotic families with massive lipoprotein elevation from the arteriosclerosis which occurs in the population at large These special individuals are developing such vascular disease very rapidly, associated with their extremely high levels of the various lipoprotein classes but inasmuch as their lipoproteins appear to be of the same chemical types as those that occur in individuals of the population at large[35] the disease in their arteries hardly deserves the special termination xanthomatosis of the arteries What every physician would like to know is the extent to which familial factors may operate in coronary heart disease *in the population at large* rather than in coronary heart disease in these special families A sound evaluation of this issue requires careful studies of one or more types A careful study could be undertaken to determine the incidence rate of coronary heart disease in siblings of persons in the population at large who have demonstrated premature clinical coronary disease instead of the incidence in siblings of selected persons from known xanthomatotic or hyperlipoproteinemic famlies A similar study could be undertaken to determine the history of coronary heart disease in the parents of a representative sample of persons with clinical coronary heart disease selected out of the population at large Thirdly the problem can be approached in a different manner by a correlation study of the family history of various individuals in a large population sample with those factors known to be associated with coronary heart disease Since the level of certain lipoproteins and the blood pressure are such factors it is important to measure the extent to which either is related if at all with the family history of coronary heart disease As a variant of this study measurements of the lipoproteins in the families of a large number of individuals chosen at random out of the population at large can be made to determine whether or not there exists a correlation in lipoprotein levels for family members in general such as is known to exist in markedly hyperlipoproteinemic and xanthomatotic families Some real progress has been made in several of these

may have biassed the outcome of the family history surveys To be sure the size of the difference in familial incidence of cardiovascular disease between Yater's myocardial infarction survivors and his traumatic injury control group is so large that a considerable bias could be tolerated without appreciably altering his conclusions concerning family history of cardiovascular disease Both studies should be regarded as providing highly suggestive evidence evidence that should be supplemented by approaches free of the potential bias inherent in retrospective questioning

A totally different avenue of approach is to determine certain bio-chemical or physiological variables in a representative sample of the population at large and *independently,* to determine the family history of longevity and cardiovascular disease for the same persons If the biochemical or physiological variables are themselves known to be factors in coronary heart disease any correlations observed would be of extreme interest Such a study is free of the objections inherent in that of the retrospective questioning of individuals with coronary disease since the determination of the biochemical variable such as the lipoprotein level and of the physiological variable such as the blood pressure is wholly independent of the questioning of the individuals Furthermore since the individuals do not know either their blood pressure value or their lipoprotein findings there is no chance for biassing in a direction either for or against a history of familial cardiovascular disease with unfavorable values of the particular variables under consideration We may be sure that in such a study *some* positive association of elevation of lipoprotein level with familial cardiovascular disease will necessarily be discovered This is so because of the existence of the well known special families previously described with either the S_f 0 20 lipoprotein elevation or with the S_f 20 100 lipoprotein elevation Inasmuch as such categories of individuals are known to have a high incidence of cardiovascular disease in their families any such cases in the population sample make for the positive association The question at hand is to what extent such families are represented in a cross sectional survey of the population at large It is certain that many such families have not been recognized and will be discovered in any cross section of the

characterizes studies of this type a failing which was carefully alluded to by Gertler and White and in their publication namely that this is in essence a *retrospective study* involving the questioning of a group of individuals who have coronary disease themselves and a group without such disease Inasmuch as it is common for patients with a particular disease to be seeking possible explanations for their own disease, it would not be surprising if the men who had clinical coronary heart disease below the age of 40 years might be more likely to remember the occurrence of such disease in members of their family Alternatively if the diagnosis had been in doubt for members of their families they might well be inclined to have remembered better the possibility that such a diagnosis was one of cardiovascular disease Any such effects operating for the patients with clinical coronary heart disease would tend to make coronary or cardiovascular disease appear more frequent in their relatives thus having the effect of biassing the result in the direction of the outcome that was observed

Yater and co workers in their classic studies of 866 cases of men with coronary heart disease between the ages of 18 and 39 years made observations analogous to those of Gertler and White They questioned 392 men who had survived a well documented typical attack of myocardial infarction while in the Army and they questioned a control group of 210 men (amputees or those hospitalized for gunshot wounds) concerning family history of heart disease Hypertension and/or coronary artery disease was reported for the immediate family of 41% of the myocardial infarction cases whereas these entities were reported in only 13% of the traumatic injury control group of men In the immediate family Yater includes father mother brothers and sisters The conclusion is the same as that arrived at by Gertler and White but unfortunately the defect in the study is identical with that in the study of Gertler and White namely the possible biassing of results due to awareness of coronary heart disease as a problem amongst the myocardial infarction survivors

Unfortunately in both the studies of Gertler and White and those of Yater and co workers it is virtually impossible to determine the extent to which the retrospective features of the studies

exclude such listed causes as accidental death or suicide However it is entirely possible that a sudden coronary occlusion could have led to a fatal accident and that illness such as coronary heart disease could have been a factor contributing to suicide Therefore it seems most reasonable to test for differences in lipoprotein levels Atherogenic Index values and blood pressures between the group of men reporting one or both parents dead as of the examination time and the group of men both of whose parents were alive at that time without any exclusion In additional special consideration was given to the group reporting death due to heart disease in either the mother or father Since often the person is unable to state what type of heart disease was the cause of death in the parent the overall category heart disease was utilized Any effects observed that are provably significant will no doubt be *underestimated* for heart disease other than coronary heart disease would not be anticipated to be associated with lipoprotein levels[38] For example rheumatic heart disease shows no association with lipoproteins Thus this entire approach is a conservative one aimed at discovering at least any *minimum* familial aspects of coronary heart disease

THE LIPOPROTEIN AND ATHEROGENIC INDEX VALUES IN RELATION TO FAMILY HISTORY

Of the 878 men between 30 and 39 years under study 421 men reported that *either the father the mother* or both were dead at the time of examination whereas 457 men reported that both parents were alive at the time of examination The mean value for all lipoprotein classes for the Atherogenic Index for the diastolic blood pressure and for the ages of the men in both groups are presented in Table XVIII It is noted that the average age of those men reporting one or both parents dead is 34 5 years whereas the average age for those men reporting both parents alive is 33 7 years Therefore it is appropriate to make the small correction in all values for the latter group for the 0 8 year difference in average age When this is done the values for each class of lipoproteins and the Atherogenic Index values

population at large The extent to which such cases will be diluted out by the very much larger group of cases not characterized by extreme derangement of lipoprotein levels or to which such cases will be supplemented by cases with a mild lipoprotein derangement familial in origin cannot be predicted in advance However a *mild* derangement in a biochemical variable or physiologic variable associated with familial cardiovascular disease should manifest itself by a shift in all parts of the distribution of cases on the particular variable to higher values for the group with a positive family history of cardiovascular disease If the only derangement that exists is that in families with the massive defect this would manifest itself instead as just a small number of cases in a tail of the distribution curve

An investigation of precisely this type has now been completed[37] including lipoprotein measurement blood pressure measurement and a family history evaluation for 878 employed men between the ages of 30 and 39 years Blood was taken for lipoprotein analysis and blood pressure measurements were made in the course of routine periodic medical employment examinations the individual being completely unaware that any such research studies were involved In a separate part of the same examination all individuals were asked to fill out a routine questionnaire concerning the presence or absence of heart disease or other diseases in their families and the cause of death if their parents were dead Numerous possible subdivisions of family history are of interest in this type of study While it would be ideal to have available documented histories concerning coronary heart disease in the parents of the population sample under study this ideal is very difficult to achieve in practise Most individuals have only a general idea of cause of death in their parents especially if such death had occurred several years ago One major criterion that is reliable is the determination of whether or not the parents are dead or alive for all the subjects under study Beyond this the information obtained becomes progressively more vague Such statements as dead of natural causes can mean just about anything but many individuals know no more than this as a cause of death in their parents In the group of deaths it might at first thought seem reasonable to

the difference in values and the significance test upon this difference are as listed below

	One or Both Parents Dead	Both Parents Alive (Corrected for Age)	Difference	Significance Test
S_f 0-12 lipoproteins	360.5	351.0	9.5	Not significant
S_f 12-20 lipoproteins	[illegible]3.0	50.8	2.2	Not significant
S_f 20-100 lipoproteins	9[illegible].0	90.5	6.5	p = 0.1
S_f 100-400 lipoproteins	57.9	48.2	9.7	p = 0.0[illegible]
Atherogenic Index	[illegible]2.4	68.1	4.3	p < 0.01

The Atherogenic Index which expresses the composite important information is clearly higher for the group with one or both parents dead than for the group with both parents alive even after correction for the slight age difference between the groups (less than one chance in 100 that random sampling would give rise to this large a difference) Therefore a family history of longevity is definitely associated with lower average Atherogenic Index values in the offspring One possible objection must be considered This is the possibility that the group with deaths in the parents may on the average be represented by parents who had their children at a later period in life But this cannot be of any consequence since by separate test it has been shown that the lipoprotein values and Atherogenic Index values in offspring are the same independent of whether either or both parents are in their twenties thirties or forties at the time of birth of their offspring Therefore the only conclusion is that a family history of early death in one or both parents is associated with higher average Atherogenic Index values in the offspring

The next question worthy of consideration is whether the observed significant effect occurs because of a few individuals with very high lipoprotein atherogenic index values or because of a *general* shift toward higher values in the offspring of parents who die at a relatively early *age* One good test of this is a determination of the fraction *of parents* dead for offspring in each Atherogenic Index category If the fraction of dead rises smoothly with increase in A I values even in the moderate A I value ranges it can be inferred that a general shift exists rather than that all the effect *is due to* the presence of a small number

TABLE XVIII

The Relationship of Parental Longevity with Lipoprotein Levels, Atherogenic Index Values and Diastolic Blood Pressures in Overtly Healthy 30-39 Year Old Men

GROUP	Number of Cases	Mean Age (years)	Mean S_f 0-12 (mg/100ml)	Mean S_f 12-20 (mg/100ml)	Mean S_f 20-100 (mg/100ml)	Mean S_f 100-400 (mg/100ml)	Mean A.I. Value (units)	Mean Diastolic Blood Pressure mm Hg
Men Reporting Both Parents Alive	457	33 7	348 6	50 0	88 9	47 0	67 3	69 2
Men Reporting One or Both Parents Dead (Death of all causes)	421	34.5	360 5	53 0	97 0	57 9	72 4	70 6

TABLE XX

THE RELATIONSHIP OF A HISTORY OF FATHER'S DEATH OF HEART DISEASE WITH LIPOPROTEIN LEVELS, ATHEROGENIC INDEX VALUES AND DIASTOLIC BLOOD PRESSURE IN OVERTLY HEALTHY 30-39 YEAR OLD MEN

GROUP	Mean Age (years)	Mean S_f 0-12 (mg/100ml)	Mean S_f 12-20 (mg/100ml)	Mean S_f 20-100 (mg/100ml)	Mean S_f 100-400 (mg/100ml)	Atherogenic Index (units)	Diastolic Blood Pressure (mm Hg)
All 8,8 Men Studied	34 1	3,4 3	51.5	92 7	52.2	69 7	69 9
1?2 Men Reporting Father was Dead of Heart Disease	34 0	366 6	54 2	110 0	75 0	78.5	72.5

of individuals with very high Atherogenic Index values. Such data are presented in Table XIX. It is evident that at least above 70 A.I. units the fraction dead is rising smoothly with increasing A.I. values, indicating that short lived parents are associated with a *general shift* toward higher A.I. values in offsprings rather than with the presence of a relatively small proportion of offsprings with extremely high A.I. values. The relationship of A.I. value in offspring to longevity in parents is by no means small since comparison of the group with A.I. values above 110 units with the group having A.I. values below 60 units shows a 52% increase *in the fraction with one or both parents dead* (0.64 compared with 0.42).

Of the 421 men in the 30-39 year age group studied, 122 men reported the father to be dead of heart disease. A highly rigorous test of the association of death of a father due to heart disease with elevation of lipoprotein level of Atherogenic Index value is to determine whether the 122 men with fathers dead of heart disease show significantly different levels from all other persons in the group (878-122 or 756). The data necessary for this comparison are presented in Table XX. The men with

TABLE XIX

RELATIVE PROBABILITY OF HAVING ONE OR BOTH PARENTS DEAD IN RELATION TO ATHEROGENIC INDEX VALUES IN 30-39 YEAR OLD MALE OFFSPRING

Atherogenic Index Range (units)	*Fraction of Subjects Having One or Both Parents Dead*	*Relative Probability of Having One or Both Parents Dead (setting value = 1.00 for A.I. values below 40 units)*
< 40	23 out of [illegible] or 0.42	1.00
40-49	50 out of 120 or 0.4[illegible]	1.00
50-59	71 out of 162 or 0.44	1.05
60-69	65 out of 1[illegible]4 or 0.42	1.00
70-79	71 out of 145 or 0.49	1.17
80-89	52 out of 94 or 0.55	1.31
90-99	31 out of 59 or 0.53	1.26
100 or higher	46 out of 80 or 0.58	1.38
110 or higher	36 out of 56 or 0.64	1.52
130 or higher	21 out of 28 or 0.75	1.79

For men of 35 years of age with A I values over 110 units there is approximately a five fold greater fraction of fathers already dead of heart disease in comparison with the fraction of fathers dead of heart disease for 35 year old men with A I values below 50 units

A similar test was carried out to determine any possible association of death of the mother of heart disease with lipoprotein and Atherogenic Index values in the offspring Unfortunately for this test but expectedly the number of men out of the total of 878 with mothers dead of heart disease was only 31 cases While the Atherogenic Index was higher (75 0 units) for the men whose mothers were dead of heart disease than for the overall group of 878 men (69 7 units) the number of cases available did not allow for proof that this difference in A I values was significant However the class of lipoproteins which had shown the most striking elevation in level for men with fathers dead of heart disease the S_f100-400 lipoproteins *could* also be proven significantly higher for the men whose mothers were dead of heart disease than for the men in the overall group (p = 0 02)

TABLE XXI

RELATIVE PROBABILITY OF HAVING FATHER DEAD OF HEART DISEASE IN RELATION TO ATHEROGENIC INDEX VALUES IN 30 39 YEAR OLD MALE OFFSPRING

Atherogenic Index Range (units)	*Fraction of Subjects Having Father Dead of Heart Disease*	*Relative Probability of Having Father Dead of Heart Disease (setting value = 1.00 for A I values below 40 units)*
< 40	3 out of 56 or 0 054	1 00
40-49	14 out of 1 1 or 0 116	2 1[illegible]
50 59	17 out of 16 or 0 103	1 91
60 69	18 out of 156 or 0 115	2 13
[illegible]0 [illegible]9	26 out of 147 or 0 179	3.28
80 89	9 out of 9 or 0 095	1 [illegible]6
[illegible]0 99	14 out of 60 or 0.233	4.32
100 o higher	1 out of 80 or 0.[illegible]63	4 87
110 or higher	16 out of 5[illegible] or 0.291	5 39
130 or higher	11 out of [illegible]8 or 0.395	7.[illegible]8

fathers dead of heart disease were on the average 0.5 years older than the overall group of 878 men (34.6 years versus 34.1 years). The various lipoprotein values and the Atherogenic Index values are readily corrected for this 0.5 year age difference. The age-corrected values and the difference between the overall group of men and that part of the group with fathers dead of heart disease, together with significance tests of such differences are listed below.

	Overall Group	Father Dead of Heart Disease	Difference	Significance Test
	(Corrected for 0.5 Year Age Difference)			
s_f0-12 lipoproteins =	354.3	365.1	10.8	Not significant
s_f12-20 lipoproteins =	51.5	53.7	2.2	Not significant
s_f20-100 lipoproteins =	92.7	109.0	16.3	$p < 0.001$
s_f100-400 lipoproteins =	52.2	71.2	22.0	$p < 0.001$
Atherogenic Index =	69.7	78.0	8.3	$p < 0.001$

These data leave little question but that the group of men whose fathers are already dead of heart disease are quite different in lipoprotein and Atherogenic Index values from the overall group of men of the same age. (For the Atherogenic Index the chance that random sampling could have given rise to the observed difference is less than one in 1000.) Here again it is of interest to know whether the effect is accounted for by a relatively small proportion of men with extremely high Atherogenic Index values or whether it is a continuous effect operating over the entire range of Atherogenic Index values encountered. In Table XXI are presented the data concerning the fraction of men in the overall group whose fathers are dead of heart disease ranked by Atherogenic Index value of the offspring. Inspection of those data indicates clearly that the effect is a smoothly continuous one over essentially the entire Atherogenic Index range with a rising fraction dead of heart disease with rising Atherogenic Index value. Thus the effect is not accounted for only by a small group of men with very high Atherogenic Index values. The comparison of the death rate due to heart disease in fathers of men with high Atherogenic Index values with that for men with very low Atherogenic Index values is startling

nary heart disease and a family history of heart disease Furthermore such evidence is free of any of the possibilities of retrospective bias that may characterize questioning men with coronary heart disease concerning the presence or absence of heart disease in their families In this study of lipoproteins Atherogenic Index and blood pressure levels versus family history there is no knowledge available to the experimental subject concerning these measurements that might have conceivably biassed his reply to the questionnaire concerning family history It is of interest that these studies free of the possibility of retrospective bias do lead to precisely the same type of conclusion arrived at by Yater and co workers and independently by Gertler and White through their retrospective studies of the family history in young men with coronary heart disease

POSSIBLE MECHANISM OF MEDIATION OF EFFECT OF FAMILY HISTORY UPON ATHEROGENIC INDEX VALUES

Establishment that the 30 39 year old offspring of fathers who die prematurely of heart disease show higher Atherogenic Index values than do members of the overall 30 39 year population sample leads immediately to the question of how such an effect is mediated A familial relationship can be on a hereditary or genetic basis or it can be the result of environmental features common to the members of a particular family It is sometimes a matter of no little difficulty to distinguish these two mechanisms Further the situation may even be complicated by the inheritance of a trait that alters the offspring s response to a particular environmental influence

In subsequent chapters two features of humans associated with lipoprotein Atherogenic Index alteration will be discussed in detail These are the degree of overweight and the cigarette smoking habit There are elements in both these features that suggest familial factors may be of consequence Overweight may conceivably be associated with hereditary tendencies to hypometabolism or to overeating or with familial patterns of overeating Cigarette smoking may conceivably be a reflection in part at least of a type of temperament that could be heritable or even

THE BLOOD PRESSURE IN RELATION TO FAMILY HISTORY

All the considerations above apply to one major factor involved in the development of coronary heart disease namely the lipoprotein Atherogenic Index value The diastolic blood pressure level is from previous discussion (See Chapter IV) the other major factor involved in determination of coronary heart disease risk Hence any possible relationship of blood pressure in offspring with family history of early death or of heart disease specifically is of importance In Table XVIII are presented the data for the diastolic blood pressures in the 421 men with one or both parents dead and for the 457 men with both parents living It is not possible to show from these data that the diastolic blood pressure is significantly different for those men with parental history of early death as compared with a parental history of longevity The second pertinent comparison is that for the 122 with fathers dead of heart disease with the overall group of 878 men *This comparison is tabulated below*

	Mean Age (Years)	*Mean Diastolic Blood Pressure (mm Hg)*
122 men with fathers dead of heart disease	34 6 years	72 5 mm
878 men (overall group)	34 1 years	69 9 mm

After correction for the 0 5 year difference in age for the group with fathers dead of heart disease (a correction of 0 2mm) the difference between this group and the overall group is 72 5 70 1 or 2 4mm *While this is a small difference in mean diastolic* blood pressure the large number of cases available allows one to be sure that there is less than one chance in 100 that this difference in blood pressures would be observed as a result of random sampling Therefore there is a low degree of positive association of elevation of diastolic blood pressure in the offspring with the history of death of the father of heart disease The magnitude of the effect is certainly less than that observed for the Atherogenic Index

The evidence presented here is strong that a positive association exists between two known factors predisposing to coro

or environmental mechanism or some combination thereof can not be determined within the framework of this evidence

The 122 men with a paternal history of death from heart disease smoked on the average 10 1 cigarettes per day The overall group smoked on the average 9 9 cigarettes per day Therefore there is no evidence that would suggest that any of the association between lipoprotein level elevation and paternal history of heart disease is at all mediated by a tendency to smoke cigarettes

THE PRACTICAL CLINICAL IMPLICATION OF ASSOCIATION OF ATHEROGENIC INDEX VALUES WITH FAMILY HISTORY OF HEART DISEASE

That a parental history of heart disease is associated with a significant elevation in Atherogenic Index value and to a lesser extent in diastolic blood pressure in offspring can now be accepted as well documented Therefore there is every reason to expect a higher incidence of coronary heart disease in persons whose parents had heart disease at a relatively early age than in persons without such a parental history Further from the data relating Atherogenic Index and blood pressure to risk of future coronary heart disease the precise extent to which a positive family history increases the average risk of coronary heart disease in offspring could readily be estimated Unfortunately however no really satisfactory unbiassed data are available to determine directly how large this association is in the population at large Thus while a higher incidence rate of coronary heart disease is definitely to be expected in the offspring of persons with heart disease it is not possible at this time to state whether or not the Atherogenic Index plus blood pressure findings account for the totality of such association as does exist In any event the evidence for the effect of family history operating via these mechanisms is solidly based and free of speculation or bias The available evidence does not allow for a statement that no other possible mechanisms might exist in addition although no comparably documented evidence supports such other possible mechanisms One possible factor that has been suggested by several workers

of a family environment that leads to smoking For overweight persons, there does exist an average elevation in Atherogenic Index arising primarily from an association of overweight with S_f20 100 and S_f100 400 lipoprotein levels For cigarette smokers the most prominent effect upon Atherogenic Index arises through the association of cigarette smoking with elevation of S_f0 12 lipoprotein levels

The elevation in Atherogenic Index in the 122 men who reported the father dead of heart disease is predominantly associated with elevation in S_f20 100 and S_f100-400 lipoprotein levels The smaller degree of elevation of S_f0 12 lipoprotein levels could not be proved significant within the existing data These findings suggest that it would be worthwhile to know whether these 122 men are overweight relative to the overall group and possibly whether they are heavier smokers Degree of overweight is expressed in terms of the value known as the relative weight which is the person s actual weight divided by the ideal weight for his height *(See Chapter IX)* The average relative weights for those with a father dead of heart disease and for the overall group of men are as follows

For 122 men with father dead of heart disease Relative Weight = 1 092
For 878 men in the overall 30 39 year old population sample
Relative Weight = 1 044
Difference = 0 048

On the relative weight scale the men whose fathers are dead of heart disease are 5% heavier than the overall group A statistical test of this difference shows that a difference this large would arise by sampling errors less than once in 10 000 times It can therefore be concluded that the men whose fathers died of heart disease are heavier for their height than are the men in the overall group From the data of Table XXXII this degree of increase in relative weight would be expected on the average to lead to an elevation in Atherogenic Index of 2 9 units The observed elevation for the 122 men with fathers dead of heart disease is 8 3 units Therefore approximately 35% of the elevation in Atherogenic Index would be expected from their degree of overweight Whether the relationship of overweight with history of paternal death of heart disease operates via a hereditary

group who e fathers were already dead of heart disease Inspection of these data shows immediately that in spite of the *shift in distribution* of Atherogenic Index values to high values there are many individuals in this group characterized by low Atherogenic Index values values lower than average for the overall population of persons of this age group Entirely similar considerations apply to the diastolic blood pressure findings If a person has essentially escaped the family history effect namely if he has a moderate or low Atherogenic Index and a moderate or low blood pressure value there exists no evidence whatever that he need fear premature coronary heart disease solely because of an unfavorable family history of such disease Even in the families characterized by one or another of the massive defects in blood lipoprotein levels such as marked s_f0 12 lipoprotein elevation or s_f20-400 lipoprote n elevation an appreciable fraction of the members of the family escape the inherited defect Thus when a father shows the lipoprotein derangement it is common to find that a daughter may show the derangement too but that one or more sons do not Alternatively a son or several sons may show the derangement whereas none of the daughters show it

The crucial clinical issue in all of this is that the physician can be if he chooses vastly more precise in his *prognostic evaluation* of the meaning of an unfavorable family history of heart disease in a particular patient It is neither correct medically nor good clinical medicine to issue a poor *prognosis* for future coronary heart disease risk to a patient simply because of an adverse family history It is not *correct to in*form a patient that his outlook is unfavorable because he has chosen his ancestor s unwisely Many such persons have far lower risks of future coronary heart disease than the average *man* in the population and this most favorable news can be transmitted to such a person by the physician who utilizes the modern simple methods of obtaining the requisite information

Nor should errors of the opposite type be made clinically It does follow from the evidence at our disposal that a favorable family history of freedom from premature heart disease means *on the average* a lower risk of future coronary heart

is the inheritance of some type of defective coronary vascular tree in persons with a positive family history of early coronary heart disease Suggestions have been made that either the intimal thickness of the coronary arteries or anatomical pecularities such origin of the arteries or kinking might be hereditary predisposing factors These are but speculations wholly unsupported by any evidence and hence hardly deserving of consideration in the practical clinical matter of dealing with patients

While the evidence is conclusive that a family history of heart disease does *on the average,* predispose the offspring to coronary heart disease via the lipoprotein and blood pressure mechanisms it cannot be stressed too much that this is an *average* predisposition By no means does every person with a family history of premature heart disease show the elevation in Atherogenic Index or diastolic blood pressure that characterizes the group as a whole In Table XXII is presented the distribution of Atherogenic Index values for the 122 men in the 30 39 year age

TABLE XXII

DISTRIBUTION OF ATHEROGENIC INDEX VALUES FOR 122 MEN (30 39 YEAR AGE GROUP) WHO REPORT THEIR FATHERS ARE DEAD OF HEART DISEASE

Range of Atherogenic Index Values (units)	*Number of Men Who Reported Father Dead of Heart Disease*	*Number of Men Who Report a History Other Than Father Dead of Heart Disease*
Below 40	3	53
40 49	14	107
50 59	17	148
60 69	18	138
70 79	26	121
80 89	9	86
90 99	14	46
100 109	5	18
110 119	4	16
120 129	1	6
130 139	6	2
140 or higher	5	15
TOTAL	122	756

Chapter VII

THE RELATIONSHIP OF AGE WITH CORONARY HEART DISEASE

There is no doubt whatever that the attack rate of clinical manifestations of coronary heart disease increases with increasing age in the American population both in the male and female sex The United States Vital Statistics reproduced below in Table XXIII clearly indicate the startling and definite rise in incidence of clinical coronary heart disease with increasing age for both sexes There exist in the clinical literature some erroneous impressions concerning the relative frequency of coronary heart disease at various ages Thus from the analysis of the age distribution of cases of myocardial infarction in office practice or in consecutive hospital admissions many authors have commented upon the fact that a particular age bracket for example 50 to 59 years appears to be that in which persons are especially prone to develop clinical coronary heart disease simply

TABLE XXIII

FATAL CORONARY HEART DISEASE INCIDENCE RATE IN NUMBER OF PERSONS PER 100,000 PER YEAR IN THE UNITED STATES

(From U S Vital Statistics 1949)

Age Group (years)	*Fatal Coronary Heart Disease Incidence Rate in Cases per 100,000 per persons per year*	
	Men	*Women*
35	49	11
45	200	52
55	656	20,
6	1705	753

disease because of a lower *average* Atherogenic Index and diastolic blood pressure. But many individuals with an excellent family history of freedom from heart disease can and do show high Atherogenic Index and blood pressure values in spite of the average trend. Therefore re-assurance of a patient of a bright outlook for freedom from coronary heart disease simply because of a good family history represents poor clinical medicine, for it may deny the individual the opportunity to discover the basis for a seriously high risk of future coronary heart disease and to take in time those steps which might reduce the risk appreciably.

have had recourse to a superficial device for solving the problem of the increasing frequency of clinical coronary heart disease with increasing age They have stated simply that coronary heart disease in the older age groups is a different disease from coronary heart disease in the younger age groups With this statement being made equivalent to a definition the difference in frequency of the disease between the older age group and the younger age group requires no special explanation Actually however recourse to such an explanation would mean that not just two diseases must be accounted for but rather many diseases for the increasing frequency of coronary disease with aging operates all the way from the third decade of life up through at least the eighth decade of life If the device is used of renaming the disease as a different entity in the older age group from that in the younger group it would be quite appropriate to state that for every ten year age span there is a different disease with which we are dealing Carried to extremes it could be stated that there is a different coronary disease at every year of life in order to explain increase in frequency with change in age It is important to note that neither clinical nor pathological evidence suggests any significant difference in the basic picture of clinical coronary heart disease between that seen at one age and at another It is not surprising that there may be minor differences in the clinical picture of coronary heart disease in a 75 year old man from that in a 25 year old man since physiologically there are many features that are different in men in the 75 year age group from men in the 25 year age group The central pathological feature noted is that of coronary artery narrowing due to an accumulation of material within the intima a feature that has been found to characterize myocardial infarction autopsy material all the way from 18 out to 80 years of age

Before considering in detail the evidence with respect to coronary heart disease itself some general concepts should be delineated concerning diseases which show an increasing frequency with increasing age especially in relationship to the evaluation of factors conceivably responsible for these observed trends The basis for a disease may be primarily a factor which operates *instantaneously* An illustration of this would be a sit

because this age bracket contains a larger number of their cases than any other single age bracket Such statistics are grossly misleading for they fail to take into account the *size of the population at risk* in the various age categories Thus if there are many more men in the population in the age group 50 59 years than there are in the age group 70 79 years there may be more hospital admissions due to coronary disease in the 50 59 year age group than the 70 79 year age group even though the risk of coronary heart disease is much higher per thousand persons per year in the older age group Data concerning the frequency of coronary heart disease in relationship with age can only be meaningful if they are expressed in reference to the population at risk namely in terms of the attack rate or the number of cases per thousand persons at risk per year or per 100 000 persons at risk per year rather than in terms of absolute number of cases admitted in a hospital per year So well known is the relationship between increase in frequency of coronary heart disease with increasing age that many writers have in the past drawn the erroneous conclusions that age is *the* factor in the development of coronary heart disease and that coronary heart disease is an inevitable accompaniment of aging To be sure the relationship of clinical coronary heart disease incidence with increasing age is highly impressive but it by no means justifies the statement that age is *the* factor or the most important factor involved nor does it justify a concept of the inevitability of development of clinical coronary heart disease with increasing age The phenomenon of occurrence of serious or fatal myocardial infarction in 35 year old men and even in 25 year old men no longer excites the special interest that it once did for we now know that many men develop such serious disease even before the age of 35 years The recent experience of Yater (during World War II) in accumulating a series of over 800 documented cases of myocardial infarction in men between the ages of 18 and 39 years is eloquent testimony to the all too great frequency of coronary heart disease even at relatively early ages

The increasing frequency of coronary heart disease with increasing age demands explanation in an over all concept of the nature of the evolution of this important clinical entity Some

increased This is true simply because for a process which operates by accumulation over time there would be a greater *accumulation* of the sub-clinical disease in 20 years than there would be in ten years in 30 years a still greater accumulation and in 40 years an even greater accumulation In a hypothetical case such as this it would be wholly incorrect to make the statement that the blood sugar level had not been important in the development of the disease simply because its average level remained the same with increasing age It could very well be the total or predominant cause of the disease As a general procedure for demonstrating that a factor which operates in this particular manner is important for a disease a group of individuals all at a particular age can be studied If it is found that those who show the higher levels of the particular factor have more of the disease under consideration than do those who show low levels this would represent strong evidence to implicate the level of the factor in the disease

The application of simple logic will often enable one to determine the manner in which a particular factor is associated with a particular disease and indeed to determine whether or not one is dealing with an *instantaneous* or an *accumulative* type of factor It is often readily possible to show that particular factors cannot possibly operate in one of the two ways e g as an instantaneous factor because assumption that it does would lead to results highly inconsistent with observational material which of course (if properly observed) must be correct At times it may not be possible from a *single* item of evidence to make the determination of whether an instantaneous factor or an accumulative factor is at hand but with consideration of several segments of the evidence a consistent picture may emerge for one type of factor e g the accumulative one but a highly inconsistent picture for the *other* e g the instantaneous one in which case the choice of the nature of the factor becomes quite clear—at least quite clear as a working hypothesis for further consideration

The specific problem of sub-clinical and clinical coronary heart disease may now be considered in the light of these general principles The detailed evidence that the lipoprotein Atherogenic Index and the blood pressure are two major factors

uation where an acutely toxic substance is ingested and instantaneously produces clinical manifestations In this case there would be no accumulation of illness over previous weeks months or years A second possible type of illness would be that where some factor operates not instantaneously but rather over a period of time With longer periods of time passed the greater is the accumulation of the sub clinical aspects of the disease and hence the greater the chance of expression of the disease in clinical form In this latter case the factor responsible can be considered to be expressive of the *rate* at which sub-clinical disease accumulates whereas the total *amount* of accumulated disease would be expressed by the multiplication of this rate factor and the time period over which it has operated Lastly, in a complex disease process there might be a combination of those factors which operate instantaneously and those factors which operate over a period of time to produce accumulation of disease at the sub clinical level If a factor operates instantaneously in the production of a disease explanation of an increasing frequency of this disease with increasing age would require that there must either be if the factor is a presence versus absence factor a progressively greater number of individuals in the population who possess this factor as age increases or if the factor is universally present but at different levels in different individuals there must be a sufficient increase in the percentage of individuals with high levels of this factor with increasing age in order to explain the age trends observed On the other hand for a factor which is expressive of the *rate* at which sub clinical disease develops it is possible for both the level of the factor and the fraction of the population characterized by each such level to remain constant over the entire usual life span of individuals and still be consistent with an increasing trend of mortality from the disease with increasing age Thus for example *if* the level of blood sugar were known to have the same distribution and the same average level for every age in life and *if* it were also known that the level of blood sugar were expressive of the rate at which some disease develops sub-clinically it would be expected that the overt expression of that disease would increase with increasing age even though the blood sugar level remained the same as age

that (1) the Atherogenic Index *cannot* operate primarily as an instantaneous type of factor (2) that it would be consistent with the observed facts to consider the possibility that the Atherogenic Index operates as an *accumulative* type of factor and (3) the possibility deserves consideration that the Atherogenic Index may still operate as an instantaneous factor but some unknown hypothetical undiscovered factor operates as a major accumulative factor Attention may now be turned to the blood pressure as a factor with demonstrated ability to predict the risk or attack rate of clinical coronary heart disease Does the blood pressure operate as an instantaneous factor in producing risk of clinical coronary heart disease or as an accumulative factor? In Table XIV is presented the relative risk or attack rate of coronary heart disease for various values of the diastolic blood pressure In order to explain a 35 fold increase in coronary heart disease attack rate that is observed for 65 year old men versus 35 year old men it would be required that the average *diastolic* blood pressure for 65 year old men be much higher than 150 mm Hg compared with the average of 71 mm Hg for 35 year old men This however is clearly not the case since the blood pressures are 76 mm Hg and 71 mm Hg for the two age groups respectively Therefore it is clearly inconsistent with reality to assume *that* blood pressure *can* be operating as an instantaneous factor to explain the difference in attack rate of coronary heart disease for these two age groups assuming the blood pressure to operate as the only or major factor in determining the risk The conclusions we can draw from this are (1) the blood pressure cannot possibly be described as an *instantaneous* factor to explain the marked increase in coronary heart attack rate with increasing age (2) it would be consistent with the evidence for the blood pressure to operate in an accumulative *fashion* producing the risk of clinical coronary heart disease and (3) it would still be consistent that the blood pressure operates *instantaneously* but that some unknown hypothetical undiscovered factor oprates in an accumulative fashion Lastly the possibility must be considered that in some way the blood pressure and the Atherogenic Index might together represent an instantaneously operating factor in the production of risk of clinical coronary heart dis

in determining the risk of clinical coronary heart disease has been presented Indeed no other factors have yet been discovered for which positive evidence exists demonstrating an association with the risk of future clinical coronary heart disease that cannot be explained either by their effect on the Atherogenic Index values or by their effect on the blood pressure This is not to say that no other independent factors will ever come to light However it would be highly pertinent, when and if any such factor is pro posed, to determine carefully whether it represents a truly new and independent factor or whether it is simply another reflec tion of the action of the blood lipoproteins and/or the blood pressure It is highly pertinent to evaluate serially both the lipoprotein Atherogenic Index value and the blood pressure with respect to operation either as instantaneous factors or as accumu lative factors

The risk of clinical coronary heart disease or the attack rate of clinical coronary heart disease for various values of the Atherogenic Index in 35 year old men is presented in Table XV From the U S Vital Statistics the separate knowledge is avail able showing that the coronary heart disease attack rate for 65 *year old men is approximately 35 times that for 35 year old men* If the Atherogenic Index value were to be an instantaneously operating factor in determining the risk of coronary heart dis ease and were the only or major factor operating it should be possible by inspection of the risk table for 35 year old men, Table XV to determine how high the average Atherogenic Index would have to be in 65 year old men in order to account for this 35 fold increase in heart attack rate It is seen that an Ath erogenic Index value of more than 150 units would be required for the average 65 year old man if the Atherogenic Index oper ated as an instantaneous factor and were the only one of conse quence However studies of numerous samples of the popula tion indicate that the average Atherogenic Index value in 65 year old men is only 68 8 units This is vastly below the required value of over 150 units Indeed the Atherogenic value of 68 8 units would give rise to a prediction of no increase in heart attack rate for 65 year old men versus 35 year old men, assuming instan taneous operation Therefore the conclusions must be drawn

that (1) the Atherogenic Index *cannot* operate primarily as an instantaneous type of factor (2) that it would be consistent with the observed facts to consider the possibility that the Atherogenic Index operates as an *accumulative* type of factor and (3) the possibility deserves consideration that the Atherogenic Index may still operate as an instantaneous factor but some unknown hypothetical undiscovered factor operates as a major accumulative factor Attention may now be turned to the blood pressure as a factor with demonstrated ability to predict the risk or attack rate of clinical coronary heart disease Does the blood pressure operate as an instantaneous factor in producing risk of clinical coronary heart disease or as an accumulative factor? In Table XIV is presented the relative risk or attack rate of coronary heart disease for various values of the diastolic blood pressure In order to explain a 35 fold increase in coronary heart disease attack rate that is observed for 65 year old men versus 35 year old men it would be required that the average diastolic blood pressure for 65 year old men be much higher than 150 mm Hg compared with the average of 71 mm Hg for 35 year old men This however is clearly not the case since the blood pressures are 76 mm Hg and 71 mm Hg for the two age groups respectively Therefore it is clearly inconsistent with reality to assume that blood pressure can be operating as an instantaneous factor to explain the difference in attack rate of coronary heart disease for these two age groups assuming the blood pressure to operate as the only or major factor in determining the risk The conclusions we can draw from this are (1) the blood pressure cannot possibly be described as an instantaneous factor to explain the marked increase in coronary heart attack rate with increasing age (2) it would be consistent with the evidence for the blood pressure to operate in an accumulative fashion producing the risk of clinical coronary heart disease and (3) it would still be consistent that the blood pressure operates instantaneously but that some unknown hypothetical undiscovered factor oprates in an accumulative fashion Lastly the possibility must be considered that in some way the blood pressure and the Atherogenic Index might together represent an instantaneously operating factor in the production of risk of clinical coronary heart dis

ease In Chapter V an explanation was given of how one can calculate the risk of clinical coronary heart disease by multiplying together the independent risks from the blood pressure data and from the Atherogenic Index data We may now consider the case of 35 year old men versus 65 year old men using the products of the two independent risks from the blood pressure and from the Atherogenic Index It is seen that using the mean values for diastolic blood pressure and Atherogenic Index for 65 year old men versus 35 year old men that the attack rate for 65 year old men would be approximately the same as the attack rate for 35 year old men which is far below the relative attack rates actually observed Hence the net conclusion that can be drawn from the blood pressure alone the Atherogenic Index alone, or a risk *accrued from their combination is that neither* of these values alone nor their combination could possibly operate as instantaneous factors in determining coronary heart disease risk It would still be consistent to consider the possibility that either alone or the two together operate as accumulative types of factors in determining the coronary heart disease risk or that some wholly undiscovered unmeasured unknown and hypothetical factor accounts for the age effect in coronary heart disease Inasmuch as neither alone nor these two factors in combination could consistently explain the observed fact of the age increase of coronary heart disease risk operating as instantaneous factors attention may be turned to the credibility that either or both may operate as accumulative factors in determination of risk Before proceeding with this a major point of scientific method and philosophy must be stated When evidence is clearly at hand that a given factor is definitely associated with a disease as such evidence is clearly at hand both for the Atherogenic Index and for the blood pressure with coronary heart disease it is completely illogical to abandon the test of whether instantaneous operation or accumulative operation of such factors can explain the observed data and to jump immediately to the possibility of a third unknown hypothetical undemonstrated unmeasured factor It behooves the investigator as a first step to test both the instantaneous and the accumulative possibilities for those factors which are known and proven It is only when

and if the factors which are known and proven cannot possibly explain the observations either on an instantaneous or an accumulative basis that some additional factor must be sought This point continues to escape many investigators Nature is complicated enough not to require that scientists and medical investigators introduce *needless* additional complications in her understanding The evidence may be evaluated in these lights Is there any inconsistency with observational data if the Atherogenic Index and the diastolic blood pressure are considered as accumulative factors in coronary heart disease risk and is there ancillary supportive evidence which suggests that such factors do or do not operate as accumulative factors?

THE ATHEROGENIC INDEX CONSIDERED AS AN ACCUMULATIVE FACTOR

It has been shown that the Atherogenic Index factor cannot operate as an instantaneous factor Would consistency with observational material be achieved by postulation that the Atherogenic Index operates as an accumulative factor? Suppose that the Atherogenic Index value of a person operates as an accumulative factor Under such circumstances one would expect that a particular Atherogenic Index operating for two years would accumulate twice as much toward the risk of coronary heart disease as that same Atherogenic Index operating over one year Correspondingly that same Atherogenic Index operating for ten years would accumulate ten times as much toward the risk of coronary heart disease as if such an Atherogenic Index had been operating for only one year The corollary of such reasoning concerning accumulative operation would be that an Atherogenic Index of 150 units will accumulate twice as much toward the risk of coronary heart disease in one year as an Atherogenic Index of 75 units and correspondingly that an Atherogenic Index of 150 units would accumulate as much in one year as an Atherogenic Index of 75 units would accumulate in two years Later we will come to discussions of possible more refined modifications of the handling of the time variable but for the moment this is an adequate approach In Chapters III and V it was

shown (Tables I and XV) that for any particular age group such as 30 39 year old males that the Atherogenic Index is markedly increased for those who develop clinical coronary heart disease over those who do not and that there is a rising risk of coronary heart disease with rising Atherogenic Index values For example at Atherogenic Index values of 150 units the future risk of coronary heart disease or the attack rate of coronary *heart disease in cases per thousand per year will be* approximately 11 2 times that for an Atherogenic Index of 75 units

Would the accumulative operation of Atherogenic Index help explain the marked increase in coronary heart disease in 65 year old men in terms of numbers of cases per thousand per year as compared with 35 year old men? For purposes of evaluation of this concept one can start with simplifying assumptions and then determine how the concept would be modified by reducing the simplifications If 75 units of Atherogenic Index operating over two years amounts to the same accumulation of risk as 150 units operating over one year such reasoning could be extended to state that 75 Atherogenic Index units operating for ten years would give rise to a total accumulation of 750 units for twenty years to 1500 units for thirty years to 2250 units and for forty years to 3000 units Now let us (for simplification) assume that the average man at age 35 years has had an Atherogenic Index value of 69 7 units for all the 35 years of his life and correspondingly let us assume that the average 65 year old man who has an Atherogenic Index of some 68 8 units had that same value for all of his life The 35 year old man with an Atherogenic Index of 69 7 units operating over 35 years would have accumulated 35x69 7 or 2 440 units toward his risk of coronary heart disease The 65 year old average man with a value of 68 8 units operating over 65 years would have accumulated 4 472 units in toto Now how do these two respective values of the number of accumulated units rate in terms of expected risk of coronary heart disease This can be approximated by reference to 35 year old men If a man were to accumulate 4 472 units (which is the value for the *average* 65 year old man) in 35 years instead of 65 years he would have had to have an Atherogenic Index value of 4 472 divided by 35 or 127 8 units The

risk tables (Table XV) show that in 35 year old men an Atherogenic Index of 127 8 units corresponds to 33 3 over 3 77 or 8 8 times as high a risk as for the average 35 year old man with an Atherogenic Index of 69 7 units Thus whereas consideration of the Atherogenic Index as an instantaneous factor leads to prediction of nearly equal risks for the average 35 year old man and the average 65 year old man the accumulation concept in its simplest form predicts an 8 8 fold higher risk for the 65 year old man which is much closer to reality It is important now to go back to the simplifying approximations that have been applied It can be demonstrated readily that the simplifying approximations have in no way materially altered the results obtained through the concept of accumulation One of the simplifying approximations made is that the man at 35 years of age with an Atherogenic Index of 69 7 units had this same Atherogenic Index all through the first 35 years of life It was also approximated

TABLE XXIV

Age Trends in Mean Atherogenic Index Values for United States Males and Females

Age (years)	Atherogenic Index (in units) Males	Females
Birth	(49)	(40)
	(49)	(40)
10	(49)	(40)
15	49.5	40.5
20	51.5	41 0
25	8 0	44
30	64 3	48.6
35	69 7	52.3
40	75.6	55.5
45	79.8	58.5
50	97	58.5
55	76.5	61 9
60	73.0	63.8
65	68 8	67.3
70	64 7	69.5
		71 7

Values in parentheses are based upon fewer than 25 cases Hence these values are not stably fixed

that the 65 year old man with an Atherogenic Index of 68 8 units had this same Atherogenic Index value throughout his entire 65 years Neither of these approximations could possibly hold for every man in the population for this would mean that the average Atherogenic Index does not change with age But from direct observation it is known that the average Atherogenic Index does change with age (see Table XXIV) It was shown (Chapter V) that persons tend very strongly to retain their *relative* ranking on the Atherogenic Index scale over a period of years throughout adult life Thus a 20 year old becoming a 22 year old tends to remain as much above or below average in Atherogenic Index as he was at age 20 Similarly a 30 year old becoming a 32 year old a 40 year old becoming a 42 year old and a 50 year old becoming a 52 year old all tend to retain their positions relative to persons of the same age categories on the Atherogenic Index scale assuming they do not change markedly in weight or develop some disease such as diabetes hypothyroidism or nephrosis Therefore the first simplifying approximation that the Atherogenic Index for a 35 year old man is the same for all the 35 years of his life may be substituted by an approximation which is extremely close to the truth because of the fact that people retain their relative ranking throughout life This close approximation would be that a man who at age 35 is average in Atherogenic Index would have had an average value of the Atherogenic Index for all periods in life before that The trend *in Atherogenic Index values from childhood through the* 8th decade of life is known from direct measurement (See Table XXIV) Therefore if the average 35 year old man shows an Atherogenic Index value of 69 7 units then at 30 years of age his Atherogenic Index would have been 64 3 units at 25 years 58 0 units at 20 years 51 5 units at 15 years 49 5 units at 10 years 49 units and approximately that same value back to the time of birth Now the total accumulation toward risk of coronary heart disease can be caculated directly This is done by considering successive five year intervals from birth out to the age of 35 years

For the interval 0 5 years of age

Average Atherogenic Index = 49 units   Accumulation is 5x49 = 245 0

For the interval 5 10 years of age
Average Atherogenic Index = 49 units — Accumulation is 5x49 = 245.0

For the interval 10 15 years of age
Average Atherogenic Index = 49.2 units — Accumulation is 5x49.2 = 246.0

For the interval 15 20 years of age
Average Atherogenic Index = 50.5 units — Accumulation is 5x50.5 = 252.5

For the interval 20 25 years of age
Average Atherogenic Index = 51.8 units — Accumulation is 5x51.8 = 274.0

For the interval 25 30 years of age
Average Atherogenic Index = 61.1 units — Accumulation is 5x61.1 = 305.5

For the interval 30 35 years of age
Average Atherogenic Index = 67.0 units — Accumulation is 5x67.0 = 335.0

Now all these five year increments can be summed up yielding a total accumulation=1 903 units In an entirely similar manner the five year increments from birth out to 65 years can be calculated and summed for the average 65 year old man yielding 4 174 units

This arithmetic provides the total accumulation for both the average 35 year old man and the average 65 year old man *without* the simplifying approximation of constant Atherogenic Index value throughout life The only approximation utilized is that a person retains on the average his *relative* ranking on the Atherogenic Index scale throughout life an approximation that is known from other considerations to be quite valid For purposes of estimation of coronary heart disease risk if the 65 year old average man had accumulated his total amount in 35 years instead of 65 years he would have had to show a much higher Atherogenic Index value throughout those 35 years What Atherogenic Index would he *have required to* have accumulated this total amount in 35 years? *Let us set this Atherogenic Index* value as x units From the trends in Atherogenic Index with age (Table XXIV) it can be stated that *the* Atherogenic Index value must have been 96% of x between 30 and 35 years 88% of x between 25 and 30 years 79% *of x between* 20 and 25 years 73% of x between 15 and 20 years 71% *of* x between 10 and 15 years 70% of x between 5 and 10 years and 70% of x between 0 and 5 years The total accumulation by 35 years is to be 4 174 units Therefore the very *simple* algebraic equation can be written

$$5(0.96x) + 5(0.88x) + 5(0.79x) + 5(0.73x) + 5(0.71x) + 5(0.70x) + 5(0.70x) = 4174$$

Solving for x we obtain 152.3 units which is the Atherogenic Index value at 35 years required to produce the same total accumulation in 35 years that the average 65 year old man accumulates in 65 years. From the risk table for 35 year old men (Table XV) an Atherogenic Index of 69.7 units corresponds to a relative risk of 3.77, whereas an Atherogenic Index of 152.3 units corresponds to a relative risk of 57.8. Therefore on the accumulation basis the average 65 year old man has a 57.8 over 3.77 or 15.3 fold higher risk of coronary heart disease than the average 35 year old man. The model described above for Atherogenic Index operating in an *accumulative* manner predicts therefore a 15.3 fold higher risk of coronary heart disease in the average 65 year old man than in the average 35 year old man, whereas the *instantaneous* operation had predicted nearly equal risks for these two men. Since the *observed* relative risk (from Vital Statistics) is 34.8 fold for 65 year old men versus 35 year old men, it is clear that the accumulative model brings us enormously closer to reality than does the instantaneous model.

However, this model so far only provides consideration of the Atherogenic Index factor. In Chapter V it was shown that the true risk for any individual of development of coronary heart disease from the known factors involved is arrived at by the *multiplication* of the risk from the blood pressure by the risk from the Atherogenic Index. Therefore it is now necessary to calculate the risk due to blood pressure as above and then to calculate the combined risks from blood pressure and from Atherogenic Index on the *accumulative* basis.

THE BLOOD PRESSURE CONSIDERED AS AN ACCUMULATIVE FACTOR

The procedure for calculation of coronary heart disease risk considering diastolic blood pressure to operate on an accumulative basis is entirely analogous to that for the Atherogenic Index. If the diastolic blood pressure operates in an accumulative fashion, then total accumulation toward risk is calculated by multiplying the diastolic blood pressure by the number of years during which that blood pressure has existed. The average blood pres

sure trends with age from birth out to the eighth decade of life are available (Table XXV) Thus for the average 35 year old man with a diastolic blood pressure of 71 0 mm Hg the average pressure between 30 and 35 years would have been 70 1 mm Hg between 25 and 30 years 68 3 mm Hg between 20 and 25 years 66 5 mm Hg between 15 and 20 years 63 7 mm Hg between 10 and 15 years 61 4 mm Hg between 5 and 10 years 60 5 mm Hg and between 0 and 5 years 60 0 mm Hg The total accumulation toward coronary disease risk for the average 35 year old man would therefore be 70 1x5 + 68 3x5 + 66 5x5 + 63 7x5 + 61 4x5 + 60 5x5 + 60 0x5 or 2 253 units in toto The same type of arithmetic for the average 65 year old man yields a total accumulation of 4 482 units If the 65 year old man were to have accumulated this total amount in 35 years instead of 65 years he would have had to have had a much higher diastolic blood pressure at 35 years of age What diastolic blood pressure would have been required? This is readily

TABLE XXV

DIASTOLIC BLOOD PRESSURE TRENDS WITH AGE FOR UNITED STATES MALES AND FEMALES

Age (in years)	*Diastolic Blood Pressure (in mm Hg)* Males	Females
Birth	(60.0)	(60 0)
	60 0	(60 0)
10	60 9	60 0
15	61.9	61 0
20	65.5	63 5
9	67.5	63 9
30	69.2	64.6
3	71.0	65.5
40	6	68 1
4	74 0	70.5
50	74 7	74.6
5	75.3	75 3
60	75.8	77 7
65	76 0	79 8
70	75 8	81 8

Values in parenthesis are estimated from fewer than [illegible] cases They are hence not statistically fixed

calculated by the same methods utilized for the Atherogenic Index The requisite blood pressure value may be designated as x mm Hg From the age trends in diastolic blood pressure values (Table XXV) the blood pressure between 30 and 35 years of age would have been (0 99x) mm Hg, between 25 and 30 years (0 96x) mm Hg between 20 and 25 years, (0 94x) mm Hg between 15 and 20 years (0 90x) mm Hg between 10 and 15 years, (0 86x) mm Hg between 5 and 10 years (0 85x) mm Hg and between 0 and 5 years (0 84x) mm Hg The total accumulation toward risk must be set equal to 4 182 units Therefore, this simple algebraic equation holds

$$(0.99x) \times 5 + (0.96x) \times 5 + (0.94x) \times 5 + (0.90x) \times 5 + (0.86x) \times 5 + (0.85x) \times 5 + (0.84x) \times 5 = 4482$$

Solving for x we obtain 141 4 mm Hg as the diastolic blood pressure required for the average 65 year old man to have accumulated as much in 35 years as he does at his actual diastolic blood pressure in 65 years From Table XIV relating blood pressure value to risk of coronary heart disease it is seen that a blood pressure of 71 0 mm Hg corresponds to a risk of 2 25 whereas a blood pressure of 141 4 mm Hg corresponds to a risk of 11 8 Therefore on the accumulative basis of operation of the blood pressure factor, the predicted risk for the average 65 year old man is 11 8 over 2 25 or 5 24 times that for the average 35 year old man This is to be contrasted with the relative risk of 3 43 over 2 25 or 1 5 times estimated for the diastolic blood pressure operating as an *instantaneous* factor It is clear that the accumulative operation of blood pressure provides a relative risk estimate much more in accord with observational data (The Vital Statistics) than does instantaneous operation of the blood pressure

THE COMBINED RISK OF CORONARY HEART DISEASE WITH BOTH ATHEROGENIC INDEX AND DIASTOLIC BLOOD PRESSURE CONSIDERED AS ACCUMULATIVE FACTORS

Since the overall risk of coronary heart disease is obtained by multiplying the risk arising from the Atherogenic Index by that arising from the diastolic blood pressure it is now appro

priate to estimate this overall risk from the estimates for each of these factors operating in an accumulative manner The Atherogenic Index operating as an accumulative factor leads to a predicted risk for 65 year old men 15 3 times that for 35 year old men The diastolic blood pressure operating as an accumulative factor leads to a predicted risk for 65 year old men 5 24 times that for 35 year old men Multiplying 15 3 by 5 24 yields a combined or overall risk for 65 year old men 80 2 times that for 35 year old men Proceeding along similar lines the expected comparison in fatal coronary heart disease rate for 45 and 55 year old men with that for 35 year old men can be calculated with Atherogenic Index and blood pressure operating as accumulative factors All these evaluations plus the observational information from Vital Statistics are presented in Table XXVI These comparisons show that this first approximation to a model of accumulative operation of Atherogenic Index and diastolic blood pressure provides predicted ratios for one age group of men compared with another age group within a factor of 2 to 2 5 of the observed ratios from U S Vital Statistics This is to be contrasted with the gross inconsistency of being approximately a factor of 35 times away from observation when the two factors are considered to operate as instantaneous ones Clearly accumulative operation provides an answer enormously closer to *reality* The fact that accumulative operation is still approximately a factor of 2 or 2 5 off from observation is hardly dis

TABLE XXVI

COMPARISON OF FATAL CORONARY HEART DISEASE INCIDENCE RATES FROM PREDICTION BASED UPON ACCUMULATIVE OPERATION OF ATHEROGENIC INDEX AND DIASTOLIC PRESSURE WITH OBSERVATIONAL DATA FROM U S VITAL STATISTICS

(MALES)

Age Group Under Comparison	*Predicted Ratio of Fatal Coronary Disease Attack Rates*	*Observed Ratio of Fatal Coronary Disease Attack Rates (U S Vital Statistics)*
65 years versus 35 years	80.2	54.8
55 years versus 35 years	34 9	13 4
45 years versus 35 years	9 4	4 1

calculated by the same methods utilized for the Atherogenic Index. The requisite blood pressure value may be designated as x mm Hg. From the age trends in diastolic blood pressure values (Table XXV) the blood pressure between 30 and 35 years of age would have been (0.99x) mm Hg between 25 and 30 years (0.96x) mm Hg between 20 and 25 years (0.94x) mm Hg between 15 and 20 years, (0.90x) mm Hg between 10 and 15 years, (0.86x) mm Hg between 5 and 10 years (0.85x) mm Hg and between 0 and 5 years (0.84x) mm Hg. The total accumulation toward risk must be set equal to 4.482 units. Therefore, this simple algebraic equation holds

$$(0.99x) \times 5 + (0.96x) \times 5 + (0.94x) \times 5 + (0.90x) \times 5$$
$$+ (0.86x) \times 5 + (0.85x) \times 5 + (0.84x) \times 5 = 4.482$$

Solving for x we obtain 141.4 mm Hg as the diastolic blood pressure required for the average 65 year old man to have accumulated as much in 35 years as he does at his actual diastolic blood pressure in 65 years. From Table XIV relating blood pressure value to risk of coronary heart disease it is seen that a blood pressure of 71.0 mm Hg corresponds to a risk of 2.25 whereas a blood pressure of 141.4 mm Hg corresponds to a risk of 11.8. Therefore on the accumulative basis of operation of the blood pressure factor the predicted risk for the average 65 year old man is 11.8 over 2.25 or 5.24 times that for the average 35 year old man. This is to be contrasted with the relative risk of 3.43 over 2.25 or 1.5 times estimated for the diastolic blood pressure operating as an *instantaneous* factor. It is clear that the accumulative operation of blood pressure provides a relative risk estimate much more in accord with observational data (The Vital Statistics) than does instantaneous operation of the blood pressure.

THE COMBINED RISK OF CORONARY HEART DISEASE WITH BOTH ATHEROGENIC INDEX AND DIASTOLIC BLOOD PRESSURE CONSIDERED AS ACCUMULATIVE FACTORS

Since the overall risk of coronary heart disease is obtained by multiplying the risk arising from the Atherogenic Index by that arising from the diastolic blood pressure it is now appro

over a period of time in order to result in the accumulation of visibly evident lesions In all the experimental animal studies which have been done over the years on the development of a lesion somewhat analogous to the human lesion of intimal arteriosclerosis it has been noted that where blood lipoprotein or lipid elevation is utilized to produce the lesion the lesions do not develop instantaneously but rather require *time* to develop Furthermore the longer the lipoprotein elevation has existed the more extensive is the development of the lesions Similarly with respect to the blood pressure factor the work of Heptinstall and co workers showed clearly that for a particular blood lipid elevation the extent to which lesion development was aggravated by the existence of hypertension was greater the longer the period of maintenance of elevated blood pressure cogent evidence for the accumulative operation of the blood pressure factor It is important to repeat here that such pathological considerations are in no way being utilized as the prime basis for the accumulation concept The general thesis rests upon its own merits specifically in connection with the problem of human coronary heart disease It is reassuring to find the concept in excellent agreement with the human pathological and experimental animal evidence

THE PRACTICAL CLINICAL IMPLICATIONS OF THE ACCUMULATIVE OPERATION OF ATHEROGENIC INDEX AND BLOOD PRESSURE IN CORONARY HEART DISEASE

Since the evidence is extremely strong that the Atherogenic Index and the blood pressure factor, operate over a period of time to increase *the risk of future* clinical coronary heart disease or to accumulate what may be referred to as additional sub clinical coronary heart disease this evidence must be reckoned with in appraising the clinical approach to the patient As an illustration suppose that a group of 20 25 year old males is being evaluated as part of a general adult screening program for assessment of the risk of *future clinical* coronary heart disease A small percentage of these 20 25 year old men will show

turbing considering the several places in this first approximation to a model that can produce some error in prediction It is likely that refinements both in the data available (including the U S Vital Statistics) and in the model itself may eliminate even the remaining discrepancy

In problems such as this not only is it pertinent to examine whether accumulative versus instantaneous operation gives better consistency with actual observations with respect to one phenomenon (here risks of fatal coronary heart disease) but also the evidence must be viewed in an over all light with respect to reasonableness There exists a large mass of additional information which argues strongly in favor of the accumulative mode of operation both of the Atherogenic Index and of the blood pressure rather than the instantaneous mode of operation For example, there are the phenomena surrounding the difference in cor ornary heart disease incidence rate between men and women phenomena which will be treated in extensive detail in the next chapter However it can be stated here that the only reasonable way in which the differences in heart attack rate between men and women can be explained in terms of the findings for the Atherogenic Index and the blood pressure is via accumulative operation rather than via instantaneous operation To return to pathological consideration (although as repeatedly emphasized in this book no special support for the over all concept is required from pathological considerations) two entities may be considered first xanthomatosis in humans and second arteriosclerosis development in experimental animals In families *demonstrating the lesion of xanthomatosis it is found that some young members of these families show the same degree of lipo* protein elevation as do other members of the family such as for example their parents The parents have fully developed large xanthomatous lesions while the younger members in the family may have minimal lesions or none at all Follow up of this phenomenon by Piper and Orrlid[34] has shown that this is a matter of passage of time If the younger members are followed over a period of time they do develop xanthomatous lesions This is direct evidence for a lesion similar to that of arteriosclerosis which indicates that high lipoprotein levels must *operate*

over a period of time in order to result in the accumulation of visibly evident lesions In all the experimental animal studies which have been done over the years on the development of a lesion somewhat analogous to the human lesion of intimal arteriosclerosis it has been noted that where blood lipoprotein or lipid elevation is utilized to produce the lesion the lesions do not develop instantaneously but rather require time to develop Furthermore the longer the lipoprotein elevation has existed the more extensive is the development of the lesions Similarly with respect to the blood pressure factor the work of Heptinstall and co-workers showed clearly that for a particular blood lipid elevation the extent to which lesion development was aggravated by the existence of hypertension was greater the longer the period of maintenance of elevated blood pressure cogent evidence for the accumulative operation of the blood pressure factor It is important to repeat here that such pathological considerations are in no way being utilized as the prime basis for the accumulation concept The general thesis rests upon its own merits specifically in connection with the problem of human coronary heart disease It is reassuring to find the concept in excellent agreement with the human pathological and experimental animal evidence

THE PRACTICAL CLINICAL IMPLICATIONS OF THE ACCUMULATIVE OPERATION OF ATHEROGENIC INDEX AND BLOOD PRESSURE IN CORONARY HEART DISEASE

Since the evidence is extremely strong that the Atherogenic Index and the blood pressure factors operate over a period of time to increase the risk of future clinical coronary heart disease or to accumulate what may be referred to as additional *sub clinical* coronary heart disease this evidence must be reckoned with in appraising the clinical approach to the patient As an illustration suppose that a group of 20 25 year old males is being evaluated as part of a general adult screening program for assessment of the risk of future clinical coronary heart disease A small percentage of these 20 25 year old men will show

extremely high Atherogenic Index values Such Atherogenic Index values imply a risk of coronary heart disease for these men which is extremely high compared to that for those 20 25 year old men who have low Atherogenic Index values Such relative risk may be in the neighborhood of 5, 10 15 or 30 times as high for the men with very high Atherogenic Index values as for men with very low Atherogenic Index values In spite of this clinically the conclusion should not be drawn that these men are all going to expire immediately from coronary heart disease For some strange reason certain workers who do not appear to understand the entire problem clearly seem to regard the fact that such men do *not* immediately drop dead of coronary heart disease as being in itself testimony adequate to refute the entire body of evidence concerning blood lipids and their relationship to coronary heart disease Indeed precisely the opposite is the correct expectation In spite of the marked elevation of the Atherogenic Index in such young individuals and of the fact that 30 men with high Atherogenic Index values will die of coronary heart disease in any specified time period for every one with a very low Atherogenic Index who dies of coronary heart disease in that same time period it is still true that the vast majority of the 25 year old men with high Atherogenic Index values will be alive in one year in five years and even in ten years This is true simply because it takes a *certain amount of time* over which very high Atherogenic Index values must operate in order to increase the risk to a point where an appreciable proportion of the men are dying per year Indeed reasonable estimates of this phenomenon have been made[39] to determine how many of these men will die each year of clinical coronary heart disease Listed in Table XXVII is the proportion of an original group of 35 year old men that will be dead of coronary heart disease in 1 5 10 15 20 and 25 years for very low Atherogenic Index values and for very high Atherogenic Index values Inspection of these data indicates that even for the very high Atherogenic Index value group at the end of 1 year well over 95% of the men still survive The entire concept predicts that this many will survive one year simply because they have not accumulated enough risk to have a higher death rate On the other hand

TABLE XXVII

PERCENTAGE OF MEN ESCAPING FATAL CORONARY HEART DISEASE IN RELATION TO AGE AND ATHEROGENIC INDEX VALUES

(For Men whose Atherogenic Indices are Determined at 35 years of age)

Atherogenic Index at 35 years of age	*% Alive 1 Year Later*	*% Alive 5 Years Later*	*% Alive 10 Years Later*	*% Alive 15 Years Later*	*% Alive 20 Years Later*	*% Alive 25 Years Later*
20	99 998	99 99	99 98	99 97	99 94	99 9?
40	99 997	99 98	99 97	99 85	99 5?	[illegible]
60	99 996	99 92	99 68	99 1	97 9	16.
80	99 98	99 75	99 0	97 3	94 8	91 1
100	99 85	98 95	97 2	89.2	81 9	,0?
1 0	99 75	98 1	95 1	89 4	80 9	?6 3
140	99.5	96 6	91 1	81.2	65 6	42 0
160	99 3	93 9	83 0	66 8	45 9	Less than 18 0
180	98 8	91 ?	?7 6	.2 1	23 3	Less than 5 0
200	98.5	86 8	64.3	3? 3	6 4	Less than 1 0

this in no way is inconsistent with the prediction that hundreds of times as many of these men will have died even in one year as is found for the men with very low Atherogenic Index values. As the accumulation goes on with passage of years at the high Atherogenic Index values the fraction of individuals who survive begins to drop off rather sharply, such that at 25 years beyond the original evaluation it is found that over 99% of the high group (A.I. = 200 units) is expected to be dead and that the death rate per year is high. However for the low Atherogenic Index group even 25 years later less than 1% is expected to be dead and the death *rate* per year is still comparatively low. The clinical maxim to be derived from this is that, for a person with a very high Atherogenic Index value at a young age the expectation is *not* that he will very shortly be dead of clinical coronary heart disease. Rather the expectation is that he has a high chance of living for several years. On the other hand it is known that he is *accumulating coronary heart disease risk* at a markedly excessive rate compared with a person with a low Atherogenic Index value and that preventive measures are clinically indicated in order to reduce the rate at which he is accumulating such risk.

The other clinical concern that the accumulation concept must develop in the physician is that with a high value of the Atherogenic Index and/or the blood pressure he has evidence of a high rate of development of sub-clinical coronary heart disease or alternatively a high rate of accumulation of risk of future clinical coronary heart disease. Since this is an accumulative process the time most favorable for attempting to intercept a high rate of sub-clinical coronary heart disease development is as early as possible in the over all development so as to prevent the actual accumulation of a high amount of sub-clinical coronary disease or to prevent the accumulative establishment of a high risk of clinical coronary heart disease. Even if at some later time the rate of accumulation were lowered this might be somewhat late. For even if the rate of accumulation is lowered at a particular point in later life such that *new* risk is not accumulating at a rapid rate the fact that a long period has passed at which such risk has been building up to make the total risk high can still result in a high coronary disease death rate for such indi

viduals The time for clinical action in this sphere is therefore early in adult life

There is one possible consideration which might alter some what the clinical conclusions that would be arrived at from the model of an accumulative type of development of coronary heart disease risk This is the all important question of the extent to which a risk once established can be reversed by alteration of those factors which lead to the risk With respect to coronary heart disease assume that as a result of an elevated blood pressure and an elevated Atherogenic Index over a period of years a man has accumulated a high risk of coronary heart disease developing clinically at any particular time in the future What is the possibility not only that his rate of accumulation of new risk will be altered if he should lower his blood pressure and his Atherogenic Index but also that the risk already accu mulated may itself decrease to some extent? Another way of ask ing this question is What is the prospect that once a certain amount of sub-clinical coronary heart disease (regarding sub clinical heart disease as the accumulation of risk of the later clinical event) has developed some of this sub-clinical coro nary heart disease is reversible? The precise answer to this question is not available at this time If some of the ancillary evidence is sought out for example that pertaining to the arte riosclerotic lesion and to the xanthomatotic lesion (a lesion which undoubtedly is closely related to that which leads to an accumu lation of sub-clinical coronary heart disease and to the accumula tion of clinical coronary heart disease risk) some highly sugges tive clues are obtained It is known that the arteriosclerotic lesion in experimental animals is definitely reversible to a large extent when the instigating factors are reduced in intensity Thus where lipoprotein elevation in experimental animals leads to the accumulation of arterial lesions it is known that not only do new lesions fail to develop when the lipoprotein levels are low ered but also that some of the accumulated lesions do show rever sal and diminution in size[49] In the author s own experience with human xanthomatotic patients in every case where lesions were developing at an appreciable rate and where large established lesions were present during the time when lipoprotein levels were

high two phenomena accompanied a lowering in lipoprotein levels First new lesions failed to develop and second old lesions already established showed marked regression and in many cases, complete disappearance The older the lesion the less chance there was for its complete disappearance when the lipoprotein lowering regimen was instituted These are illustrations showing that for lesions associated with coronary heart disease the reduction in intensity of factors which determine the rate of accumulation of the lesion not only had the effect of reducing the rate of *new* accumulation but also the effect of allowing reversal mechanisms to exceed development rates with resulting regression of established lesions Whether or not one should translate such evidence *directly* for the case of coronary heart disease risk is immaterial The precise possible rate of any reversal of accumulated coronary disease risk cannot be evaluated at the present time although efforts are being made to set up models and to test concepts in this direction Until such evidence can be clearly crystallized and until the exact extent to which reversal of any established risk of future clinical coronary heart disease can be mitigated by altering the current accumulation is known it would certainly seem on the side of a clinical prudence to count very little on the reversal of already established risk Every energy should therefore be centered upon the earliest possible lowering of the rate of accumulation of *new* risk It should be obvious that if one starts with 60 year old men to determine whether they have a high risk of coronary heart disease as a result of an elevation in Atherogenic Index and an elevation in blood pressure they have had a very long period of years in which *high levels* may *have* operated and hence *have contributed* to an already existing large risk of clinical coronary heart disease Therefore while it would certainly be reasonable to attempt to reduce the rate of accumulation of new risk in such men it should also be expected that even for a regimen which lowers the Atherogenic Index drastically and which lowers the blood pressure to a *very satisfactory range* many such men will still go on to develop clinical and fatal coronary heart disease as a result of their *already accumulated high risk* If 50 year old men with the same Atherogenic Index and blood pressure values

are considered the outlook is more favorable since they have had ten fewer years in which to accumulate risk due to these high values It would be clinically very helpful to apply preventive medicine for 50 year old men rather than for 60 year old men Extension of such reasoning makes it quite obvious that if men have already identified themselves at least with respect to one of these factors the Atherogenic Index by the time they are in their twenties the ideal time to start lowering the risk of clinical coronary heart disease precisely because of the age related accumulative character of coronary disease risk is at that time The age related accumulative character of coronary disease risk underlines the real place for medicine to attack the problem of coronary heart disease To be sure *established* clinical coronary heart disease must be treated in any particular patient who already has this disease for he is justifiably primarily concerned about established clinical coronary heart disease However more rewarding clinical results can be expected from the treatment of a person *before* he becomes a patient with overt coronary heart disease In few medical problems does the evidence argue more strikingly in favor of a preventive approach rather than a therapeutic approach to the disease than it does in the case of coronary heart disease This will require a considerable re-orientation in the thinking of the physician and of the public with respect to *who* is a patient Patients of real importance with respect to clinical coronary heart disease are not patients with established disease but rather the entire adult population of the United States Since there exists no simple way to know without actually making the determinations who the persons are with elevated blood pressures or elevated Atherogenic Index values or both and who hence are accumulating coronary heart disease risk at the most rapid rate it will be essential to consider as patients or potential patients every adult in the population

high two phenomena accompanied a lowering in lipoprotein levels First, new lesions failed to develop and second old lesions already established showed marked regression and in many cases complete disappearance The older the lesion the less chance there was for its complete disappearance when the lipoprotein lowering regimen was instituted These are illustrations showing that for lesions associated with coronary heart disease the reduction in intensity of factors which determine the rate of accumulation of the lesion not only had the effect of reducing the rate of *new* accumulation but also the effect of allowing reversal mechanisms to exceed development rates with resulting regression of established lesions Whether or not one should translate such *evidence directly for the case of coronary heart disease risk* is immaterial The precise possible rate of any reversal of accumulated coronary disease risk cannot be evaluated at the present time although efforts are being made to set up models and to test concepts in this direction Until such evidence can be clearly crystallized and until the exact extent to which reversal of any established risk of future clinical coronary heart disease can be mitigated by altering the current accumulation is known it would certainly seem on the side of a clinical prudence to count very little on the reversal of already established risk Every energy should therefore be centered upon the earliest possible lowering of the rate of accumulation of *new* risk It should be obvious that if one starts with 60 year old men to determine whether they have a high risk of coronary heart disease as a result of an elevation in Atherogenic Index and an elevation in blood pressure they have had a very long period of years in which high levels may have operated and hence have contributed to an already existing large risk of clinical coronary heart disease Therefore while it would certainly be reasonable to attempt to reduce the rate of accumulation of new risk in such men it should also be expected that even for a regimen which lowers the Atherogenic Index drastically and which lowers the blood pressure to a very satisfactory range, many such men will still go on to develop clinical and fatal coronary heart disease as a result of their *already accumulated high risk* If 50 year old men with the same Atherogenic Index and blood pressure values

Statistics to confirm these major differences in heart attack frequency for men as compared with women Every physician is well aware of this difference and indeed as mentioned above some have thought the differences even much larger than those which really exist In the experience of many physicians the occurrence of documentable clinical coronary heart disease in the form for example of myocardial infarction in a woman below the age of 40 years is so rare that the initial impression of some physicians is to discount the possibility of this diagnosis except under certain special circumstances Coronary heart disease can and does occur in women even at young ages but it is indeed relatively infrequent as compared with its incidence in men Where do we go with this type of information? Obviously when a dramatic feature of a disease such as coronary heart disease reveals itself such as by showing a major sex difference in incidence there exists the possibility that an understanding of the basis for this sex difference may lead to great clarification in understanding over all aspects of the disease process itself In consideration of the male female difference in coronary heart disease incidence and its possible basis let us outline the salient features which observational material has provided These are as follows

1 Early in adult life the incidence of clinical coronary heart disease and fatality therefrom is approximately four or five times in men compared with women

2 There is a progressive decrease in this ratio of attacks fatalities and incidence of clinical coronary heart disease between men and women with advancing years such that in approximately the eighth decade the incidence rate approaches equality

3 The incidence of hypertension as a factor in the development of clinical coronary heart disease seems to be distinctly more prominent in the female sex than in the male (see Chapter IV)

4 The incidence of diabetes mellitus as a factor in predisposing women to heart attacks seems to be greater than that in men

All of these salient points concerning the differences in coro

Chapter VIII

THE DIFFERENCE BETWEEN MEN AND WOMEN WITH RESPECT TO CORONARY HEART DISEASE

MEN IN THE United States unquestionably have a higher frequency of manifestations of coronary heart disease clinical and fatal then do women No single fact concerning the occurrence of coronary heart attacks is more striking to the physician viewing this over all problem To some extent the difference between men and women with respect to coronary heart disease incidence has been exaggerated in several sources possibly due to bias in the type of material observed However the data available through the United States Vital Statistics concerning the comparative heart attack rates for men and women clearly indicate that at least for relatively youthful groups the frequency of such heart disease in men greatly exceeds that in women with that difference *shrinking progressively with increasing age* These data were presented in Table XXIII Not only do the data presented there indicate that men on the average have a greater incidence rate of coronary heart disease than do women at several ages but certain other tremendously striking features of this difference emerge Whereas in the age decade from 30 39 years the incidence of fatal clinical coronary heart disease is some 4 5 times in men that which occurs in women with each passing decade the difference between men and women shrinks so that by the time the seventh decade of life is reached the incidence rate in men is approximately 2 3 times that for the women That these differences are real for the population in the United States and for the present era is beyond question There is certainly no further proof or evidence required beyond the U S Vital

value and that which obtains from the blood pressure value Therefore it will be necessary to consider not one but both of these factors in determining the risk differences between men and women at various ages

THE BLOOD LIPOPROTEIN (ATHEROGENIC INDEX) FACTOR IN MEN AND WOMEN

Measurements for the S_f 0-12 12-20 20-100 100-400 lipoprotein classes and the derived Atherogenic Index values are available for men and women at ages up to 70 years of age Such information is presented in Table XXVIII for these lipoprotein classes The Atherogenic Index data are in Table XXIV Certain facts are clear Whereas the lipoprotein levels are not strikingly different in early life[41] there is a sharp divergence in blood lipoprotein levels between the sexes in the teens and in the twenties with the males showing higher values of all four important classes of lipoproteins and of the Atherogenic Index than do the females Whereas the males show steep rises in level of the various lipoprotein classes during the third decade of life the females on the average lag behind although there is a slow rise in lipoprotein levels At a somewhat later age when the men are levelling out in average value for the various lipoprotein classes and even showing declining values the women are showing a marked increase in values until finally for each lipoprotein class there is reached an age differing somewhat for the various lipoprotein classes at which the average level in women becomes equal to the average level in men After that age the average lipoprotein level in women is higher than the average level in men For the Atherogenic Index which summarizes all the lipoprotein information with respect to coronary heart disease the age at which the average woman reaches the Atherogenic Index possessed by the average man is 61 5 years Thereafter women show on the average higher Atherogenic Index values than do men at least out to the eighth decade of life Inspection of the data reveals further that the major differences between the male and the female sex are in the lipoprotein classes of high flotation rate namely in the S_f 12 20 in the S_f 20 100 and

nary heart disease between men and women deserve careful evaluation for whatever leads they may provide with respect to the over all genesis of coronary heart disease. Possible explanations for these major observations which surround the difference between coronary heart attack rate in men and women fall into two possible categories (1) The differences observed can be explained on the basis of those factors already known and established to be associated with coronary heart disease namely the level of certain important lipoprotein classes in the blood (expressed as the composite value the Atherogenic Index) or the level of the diastolic blood pressure or both. Or (2) Certain wholly new and independent factors which have not as yet been evaluated are operative.

The proper approach to this problem scientifically is to determine *first* whether or not either known factor the lipoprotein levels or the blood pressure explains the described male female difference in all its manifestations completely or in part. If these major known factors explain the difference *completely* then there is no reason whatever to go on to the second possibility namely the search for unknown untested unheard of additional factors since there would be nothing for such factors to explain. Any such search would then be fruitless and a waste of time. It is axiomatic in science for this type of problem that when certain known factors of independent merit associated with a disease exist and when a new observation arises for consideration one tests whether the new observation is truly new or whether it can be explained by operation of the existing known factors. Any other approach to such a problem is certainly not sound scientific methodology for it essentially negates the existence of all knowledge already developed. Therefore the primary step in this evaluation is a determination of whether or not the lipoprotein factor or the blood pressure factor or a combination of these two explains any part or all of the difference in male female incidence of coronary heart disease. If such factors do *not* explain the differences observed it would then be *necessary* to go on to other possible explanations. Total risk of coronary disease arising from established factors is best expressed by multiplication of the risk that obtains from the Atherogenic Index

value and that which obtains from the blood pressure value Therefore it will be necessary to consider not one but both of these factors in determining the risk differences between men and women at various ages

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Measurements for the sf0 12 12 20 20 100 100-400 lipo protein classes and the derived Atherogenic Index values are available for men and women at ages up to 70 years of age Such information is presented in Table XXVIII for these lipo protein classes The Atherogenic Index data are in Table XXIV Certain facts are clear Whereas the lipoprotein levels are not strikingly different in early life[41] there is a sharp divergence in blood lipoprotein levels between the sexes in the teens and in the twenties with the males showing higher values of all four impor tant classes of lipoproteins and of the Atherogenic Index than do the females Whereas the males show steep rises in level of the various lipoprotein classes during the third decade of life the females on the average lag behind although there is a slow rise in lipoprotein levels At a somewhat later age when the men are levelling out in average value for the various lipoprotein classes and even showing declining values the women are show ing a marked increase in values until finally for each lipopro tein class there is reached an age differing somewhat for the various lipoprotein classes at which the average level in women becomes equal to the average level in men After that age the average lipoprotein level in women is higher than the average level in men For the Atherogenic Index which summarizes all the lipoprotein information with respect to coronary heart dis ease the age at which the average woman reaches the Atherogenic Index possessed by the average man is 64 5 years Thereafter women show on the average higher Atherogenic Index values than do men at least out to the eighth decade of life Inspec tion of the data reveals further that the major differences between the male and the female sex are in the lipoprotein classes of high flotation rate namely in the sf12 20 in the sf20 100 and

TABLE XXVIII

AGE TRENDS FOR THE VARIOUS LIPOPROTEIN CLASSES IN UNITED STATES MALES AND FEMALES*

Lipoprotein Classes

Age** (years)	Mean S_f0 12 mg/100ml		Mean S_f12 20 mg/100ml		Mean S_f20 100 mg/100ml		Mean S_f100-400 mg/100ml	
	Males	*Females*	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*
20	300 0	276 0	30 0	28 0	62 9	41 1	28 0	6 7
25	319 0	293 0	38 7	32.5	73 1	46 9	36.2	9 3
30	338 3	310.5	45 8	31 9	83 0	52 5	41 3	11 8
35	357 0	326.5	51 6	41 1	92 9	58 1	52 4	14 0
40	372 0	338 7	55 1	45.2	101 8	61 3	60 7	16 3
45	381 0	319 6	57 2	48 5	109 1	70 6	67 6	18 9
50	389 0	358 0	57 3	51 3	110 9	77 3	65 6	21 8
55	383.5	361 5	56 2	53.5	103 5	81 3	57 8	21 7
60	373 6	369.2	54 [illegible]	55 8	91 3	91 0	50 0	27 3
65	363.5	372 7	52 0	57 9	79.2	97 1	41 8	29.5
70	353 3	375 0	49 7	59 7	68 0	101 9	33 8	31 5

* Recent mean values for lipoprotein levels in women above 30 years especially of S_f20 400 classes are lower than earlier published values The recent values are for employed women at the University of California (Livermore) whereas published values are primarily for women in Framingham A best value is reported here between the two sets Framingham women have appreciably higher relative weights than do the recently studied employed women

** Data for lipoprotein levels below 20 years of age are based upon a small series of cases and are hence not reproduced here See reference 41 for approximate values

very strikingly in the sf100-400 lipoproteins From the lower Atherogenic Index values maintained in the youthful years of adult life by the average woman as compared with the average man and from the fact that the entire distribution of values in women as compared with men is shifted toward lower values it can be immediately predicted that the heart attack rate should be lower in the female sex during the young adult years than it is in the male sex The next question to consider is *how much* lower it is predicted to be In a previous chapter it was shown that the most consistent explanation of the relationship of coronary heart disease risk with Atherogenic Index and blood pressure require that these factors both operate in an *accumulative* man ner rather than as instantaneous factors Therefore in analysis of this problem concerning the male female difference in coro nary heart disease incidence we may treat the Atherogenic Index values in the male and female on the accumulative basis to deter mine how much of the excessive risk which characterizes the male sex is thereby explained At 35 years of age the men show a coronary heart disease incidence rate approximately 4 5 times that of women (U S Vital Statistics) In Chapter VII it was demonstrated by consideration of successive five year age inter vals that the average 35 year old man has accumulated 1903 units toward his risk of coronary heart disease that is for the portion of total risk which arises via the Atherogenic Index value A calculation of the number of units accumulated by the average female during the first thirty five years of life proceeds along precisely similar lines For the average female the trends in Atherogenic Index values with age are such that between 30 and 35 years the Atherogenic Index value is 50 4 units at 25 to 30 years it is 46 7 units at 20 to 25 years it is 42 8 units at 15 to 20 years it is 40 7 units at 10 to 15 years it is 40 3 units at 5 to 10 years it is 40 units and between 0 and 5 years it is 40 units Therefore the total accumulation for the average woman at 35 years of age is expressed in the following simple algebraic equation

Total accumulation = 5x50 4 + 5x46 7 + 5x42 8 + 5x40 7 + 5x50 3 + 5x40 0 + 5x40 0 = 1505 units

Now to compare the average female with the average male at 35 years in terms of coronary heart disease risk it is necessary

to determine what Atherogenic Index a 35 year old man would have to have if he were to have accumulated 1505 units by 35 years (which is what the above calculation shows that the average woman has accumulated in her first 35 years of life) We may set this required Atherogenic Index value for a 35 year old male at x units and then solve for x From the trend of Atherogenic Index with age for men it is known that between 30 and 35 years such a man would have had an Atherogenic Index value = 96% of x, between 25 and 30 years 88% of x between 20 and 25 years 79% of x between 15 and 20 years 73% of x between 10 and 15 years 71% of x between 5 and 10 years, 70% of x, and between 0 to 5 years 70% of x

The total accumulation = 5x (0 96 (x)) + 5x (0 88 (x)) + 5x (0 79 (x)) + 5x (0 73 (x)) + 5x (0 71 (x)) + 5x (0 70 (x)) + 5x (0 70 (x))

But this total accumulation is being set equal to 1505 units Solving for x yields 54 9 units which is the Atherogenic Index value a man would have to have at age 35 years to have accumulated as much as has the *average* woman by age 35 years From Table XV it is now possible to determine how the coronary heart disease risk for this Atherogenic Index value, 54 9 units compares with the risk for an Atherogenic Index of 69 7 units (which is the average value for men at 35 years The two relative risks are 2 20 and 3 77 Therefore with accumulative operation of the Atherogenic Index the risk tables predict that the average 35 year old man has 3 77 over 2 20 or 1 71 times the cornary heart disease risk of the average 35 year old woman There is a more refined method for calculating the relative risk of 35 year old men versus 35 year old women based upon calculation of average risk directly instead of the risk of the person with the average Atherogenic Index value However such a refined calculation does not materially alter the relative risk for 35 year old men versus 35 year old women obtained above Thus, Atherogenic Index alone operating as an accumulative factor leads to the expectation of a 1 71 fold coronary heart disease risk in men of 35 years as compared with women 35 years of age But this accounts only for the effect of one of the major known factors determining the risk of coronary heart disease The other factor the blood pressure must be evaluated

before the overall prediction can be compared with observational *data*

THE CONTRIBUTION OF THE BLOOD PRESSURE EFFECT TO THE DIFFERENCE IN CORONARY HEART DISEASE INCIDENCE BETWEEN MEN AND WOMEN

The contribution of the diastolic blood pressure to the difference in coronary heart disease risk between 35 year old men and women proceeds along lines similar to those for the Atherogenic Index contribution with the diastolic blood pressure to be considered as an accumulative factor The average blood pressure trends for men from birth out to late age are available in Table XXV For the average 35 year old man the diastolic blood pressure is 71 0 mm Hg The average 35 year old woman has a diastolic blood pressure of 65 3 mm Hg From the trend of blood pressure with age for the female sex it can be estimated that between 30 and 35 years this woman had a diastolic pressure of 65 0 mm Hg between 25 and 30 years 64 2 mm Hg between 20 and 25 years 63 7 mm Hg between 15 and 20 years 62 2 mm Hg between 10 and 15 years 60 5 mm Hg between 5 and 10 years 60 0 mm Hg between 0 and 5 years 60 0 mm Hg Therefore for this average 35 year old woman the total accumulation toward coronary heart disease risk from diastolic pressure as an accumulative factor = 5x65 0 + 5x64 2 + 5x63 7 + 5x62 2 + 5x60 5 + 5x60 0 + 5x60 0 or = 2178 units In order to use the Table for relative risk of coronary heart disease versus diastolic pressure (which is based upon data for men) it is necessary now to calculate what diastolic pressure a man would have to have at 35 years if he is to have accumulated as many total units (2178) during 35 years as have been accumulated by the average 35 year old woman Let x be the value of this required diastolic blood pressure Then between 30 and 35 years such a man s pressure would be 0 99 x between 25 and 30 years 0 96 x between 20 and 25 years 0 94 x between 15 and 20 years 0 90 x between 10 and 15 years 0 86 x between 5 and 10 years 0 85 x and between 0 and 5 years 0 84 x The total accumulation by 35 years of age would be

$$5(0\,99\,x) + 5(0\,96\,x) + 5(0\,94\,x) + 5(0\,90\,x) + 5(0\,86\,x) + 5(0.85\,x) + 5(0.84\,x)$$

to determine what Atherogenic Index a 35 year old man would have to have if he were to have accumulated 1505 units by 35 years (which is what the above calculation shows that the average woman has accumulated in her first 35 years of life) We may set this required Atherogenic Index value for a 35 year old male at x units and then solve for x From the trend of Atherogenic Index with age for men it is known that between 30 and 35 years such a man would have had an Atherogenic Index value = 96% of x between 25 and 30 years, 88% of x, between 20 and 25 years 79% of x between 15 and 20 years 73% of x, between 10 and 15 years 71% of x between 5 and 10 years 70% of x and between 0 to 5 years, 70% of x

$$\text{The total accumulation} = 5x(0.96\,(x)) + 5x(0.88\,(x)) + 5x(0.79\,(x)) + 5x(0.73\,(x)) + 5x(0.71\,(x)) + 5x(0.70\,(x)) + 5x(0.70\,(x))$$

But this total accumulation is being set equal to 1505 units Solving for x yields 54 9 units, which is the Atherogenic Index value a man would have to have at age 35 years to have accumulated as much as has the *average* woman by age 35 years From Table XV it is now possible to determine how the coronary heart disease risk for this Atherogenic Index value 54 9 units compares with the risk for an Atherogenic Index of 69 7 units (which is the average value for men at 35 years The two relative risks are 2 20 and 3 77 Therefore with accumulative operation of the Atherogenic Index the risk tables predict that the average 35 year old man has 3 77 over 2 20 or 1 71 times the cornary heart disease risk of the average 35 year old woman There is a more refined method for calculating the relative risk of 35 year old men versus 35 year old women based upon calculation of average risk directly instead of the risk of the person with the average Atherogenic Index value However such a refined calculation does not materially alter the relative risk for 35 year old men versus 35 year old women obtained above Thus, Atherogenic Index alone operating as an accumulative factor leads to the expectation of a 1 71 fold coronary heart disease risk in men of 35 years as compared with women 35 years of age But this accounts only for the effect of one of the major known *factors determining the risk of coronary* heart disease The other factor the blood pressure must be evaluated

culated for 45 year olds for 55 year olds and for 65 year olds These predictions and their comparison with the observational data from U S Vital Statistics are presented in Table XXIX The agreement based upon the accumulation model can be considered excellent It has been proposed that a difference in the thickness of the intimal lining of the coronary arteries may be a factor helping to account for the male female difference in coronary heart disease incidence but no real development of any significance has come from this proposal Another factor proposed concerns the so-called susceptibility of the coronary arteries to the deposition of lipids the postulation being made that such susceptibility is under the influence of estrogenic hormone Again this highly speculative proposal has no evidence which appears to substantiate it Undoubtedly other factors will be and have been proposed At the present time such factors are speculative and without any distinct evidence to support them

TABLE XXIX

COMPARISON OF FATAL CORONARY HEART DISEASE INCIDENCE RATE FOR MEN VERSUS WOMEN ESTIMATED FROM ATHEROGENIC INDEX PLUS DIASTOLIC BLOOD PRESSURE WITH OBSERVATIONAL DATA FROM U S VITAL STATISTICS

Age Group (years)	*Predicted Ratio of Fatal Coronary Heart Disease (Men/Women)*	*Observed Ratio of Fatal Coronary Heart Disease Rate (Men/Women)*
35	2.10	4.45
45	2.[illegible]9	3.85
55	[illegible]	3.20
65	2.69	2.26

THE BASIS FOR THE HIGHER FREQUENCY OF HYPERTENSION IN WOMEN DEVELOPING CORONARY HEART DISEASE IN COMPARISON WITH MEN DEVELOPING CORONARY HEART DISEASE

In Chapter IV it was pointed out that nearly every reported study in the literature shows elevation in blood pressure to be a more frequent occurrence in the women who develop coronary

But this is to be set equal to the total accumulation for the average 35 year old woman which is 2178 units

Therefore 31 7x = 2178 or x = 68 7 mm Hg which is the diastolic pressure required at 35 years for the man who has accumulated from diastolic blood pressure as much toward coronary heart disease risk as has the average 35 year old woman This man is to be compared with the average 35 year old man For a diastolic *pressure of 68 7 mm Hg the relative risk of coronary* heart disease (from Table XIV) is 1 83 x that for the reference value of 50 mm Hg whereas for a diastolic pressure of 71 0 mm Hg such relative risk is 2 25 x that for the reference value of 50 mm *Therefore the a*verage man of 35 years has *2 25* over 1 83 = 1 23 times the risk of coronary heart disease that a 35 year old man with a diastolic blood pressure of 68 7 mm However, this latter man was a calculated man to provide the same accumulative value from diastolic pressure that characterizes the average 35 year old woman Therefore diastolic blood pressure alone operating as an accumulative factor leads to a prediction that the average 35 year old man should show 1 23 times the risk of future clinical coronary heart disease that the average 35 year old woman shows

THE COMBINED EFFECT OF THE DIASTOLIC BLOOD PRESSURE AND ATHEROGENIC INDEX OPERATING AS ACCUMULATIVE FACTORS IN CORONARY HEART DISEASE IN MEN AND WOMEN

From the Atherogenic Index alone the relative risk for the average 35 year old man compared with the average 35 year old woman is 1 71 times as high and from the blood pressure the relative risk *for the man compared with the woman is* 1 23 times as high As developed in Chapter V the best approximation to *overall risk* of coronary heart disease is obtained by multiplication of the risk from Atherogenic Index by that from diastolic blood pressure *Therefore the overall risk for the* 35 year old man is calculated to be 1 71x1 23 or 2 10 times that for the average 35 year old woman By entirely similar methods the predicted coronary disease risk for men versus women may be cal

The overall coronary heart disease risk was then determined for each person in the usual manner namely *multiplication* of the risk from Atherogenic Index by that from blood pressure These overall coronary heart disease risks were then ranked from the highest to the lowest in separate lists for the men and the women For convenience each group of 100 persons can be sub divided into ten risk categories each containing ten persons and the median risk for each category calculated for the ten persons in that category Such data are presented in Table XXX ranked from the lowest risk category to the highest for each sex Now our 100 men and 100 women are each sub-divided into 10 sub groups for each sub-group the median risk being known and the distribution of blood pressures being known Suppose now that a very large population sample of 50 59 year old persons were studied during a period when they are overtly healthy In a person of time of observation de novo clinical coronary heart disease will develop in each of the 10 sub-categories of overall risk *the number* of cases in each category being directly pro-

TABLE XXX

RANKING OF 50 59 YEAR OLD MEN AND WOMEN UPON MEDIAN CORONARY DISEASE RISK

(10 Categories for Each Sex)

	MEN Median Risk (setting lowest category = 1.00)	*WOMEN* Median Risk (setting lowest category = 1 00)
Lowest Category of 10	1 00	1.00
2nd	2 35	1 88
3rd	2 77	2.09
4th	3 19	2 61
5th	4.25	2 94
6th	6 23	4.00
7th	9.31	4.58
8th	13 08	5 85
9th	18 6	9 64
Highest	50.96	16 94

Relative risks were calculated from the tables of Chapter V in the usual fashion Since the subdivision into ten categories is arbitrary the risk of all categories is presented in terms of the number of times that risk is compared with the risk of the lowest category

heart disease at a particular age than in the men who do so So marked has been this difference in some series that the authors had erroneously concluded that hypertension is not a factor in the development of coronary heart disease in men but is a major factor in its development in women Hypertension has been conclusively shown to be a major factor in the development of coronary heart disease *both* in men and women Indeed there exists no reason to believe there is any lack of equivalence of a particular degree of blood pressure elevation with respect to acceleration of sub-clinical coronary heart disease development in men versus women Why then should hypertension be a more frequent finding in women who experience clinical coronary heart disease than in men who develop that disease? Fortunately, there now exists sufficient quantitative information concerning the factors which determine the risk of clinical coronary heart disease in men and women to provide the answer to this highly important question

From the relationship of coronary heart disease incidence rate with Atherogenic Index and diastolic blood pressure it should be possible to *calculate* whether or not hypertension should be a more frequent finding in coronary heart disease among women than among men This calculation is additionally illustrative of some of the uses of risk data and is presented in detail A random sample of 100 men and 100 women in the age decade 50 59 years from a larger sample of the population study at Framingham Massachusetts was selected for this analysis For each person the Atherogenic Index and the diastolic blood pressure were available Therefore for each person the risk of future coronary heart disease can be estimated utilizing the appropriate risk tables (Table XIV and Table XVI) Before using the risk versus Atherogenic Index table for 50 59 year men to calculate the risks for the women the equivalent Atherogenic Index for men to accumulate by 55 years the same total number of units accumulated by a woman with a particular Atherogenic Index value had to be determined This was described in detail in Chapter VII Then both for the 100 men and the 100 women the coronary heart disease risk arising from Atherogenic Index and from *diastolic blood pressures were calculated* separately

the lowest risk category Now for each category the total number of cases and the number in each category with diastolic pressures above 110 mm Hg are as follows

Lowest category 100 *total* cases of which 0 have pressures above 110 mm Hg
2nd category 188 total cases of which 0 have pressures above 110 mm Hg
3rd category 909 total cases of which 0 have pressures above 110 mm Hg
4th category 61 total cases of which 0 have pressures above 110 mm Hg
5th category 94 total cases of which 9 have pressures above 110 mm Hg
6th category 400 total cases of which 40 have *pressures* above 110 mm Hg
7th category 458 total cases of which 0 have pressures above 110 mm Hg
8th category 58 total cases of which 11 have pressures above 110 mm Hg
9th category 864 total cases of which 2 9 have pressures above 110 mm Hg
10th category 1691 total cases of which 08 have *pressures* above 110 mm Hg

The total number of de novo cases of coronary disease in women is obtained by adding those in each category yielding 5053 cases Of these 953 will be characterized by pressures above 110 mm Hg This *represents 18 9%* of the total group Therefore all these calculations lead to the conclusion that 18 9 over 11 2 or *1 7 times* as many women of 50 59 years of age developing coronary heart *disease* would have shown pre-coronary pressures above 110 mm Hg as would men of 50 59 years of age who develop coronary heart disease Utilizing a blood pressure of 120 mm Hg it is calculated that 16 0% of women who develop coronary heart disease would have shown diastolic blood pressures above 120 mm Hg whereas only 0 4% of men of the same age group who develop coronary disease would have shown *pressures* above 120 mm Hg The direction of the effect and the general order of magnitude of the increase in frequency of hypertension in coronary disease in women versus men predicted from Atherogenic Index Blood Pressure risk *estimates* is therefore in accord with observational experience Precise estimation of the difference would of *course* be better obtained by the study of much larger population *samples* Thus while the very calculation itself takes *cognizance* of the importance of blood pressure as a risk factor *for both sexes* the concept still provides consistency with the observational experience that hypertension is a more *frequent* accompaniment of coronary heart disease in women than in men Qualitatively this could have been anticipated from the fact that men and women *are* more nearly alike up to 55 years of age in blood pressure than in Atherogenic Index Hence

portional to its risk Thus if for the men we wait until 100 cases of de novo coronary disease arise out of the *lowest category* the data of Table XXX inform us that in the same time interval there will be the following number of de novo coronary heart disease cases in the other nine categories

If lowest category develops 100 cases then

2nd category develops	235 cases
3rd category develops	277 cases
4th category develops	319 cases
5th category develops	423 cases
6th category develops	623 cases
7th category develops	931 cases
8th category develops	1 308 cases
9th category develops	1 865 cases
10th category develops	5 096 cases

The total number of cases of de novo coronary heart disease is obtained by adding all the cases together yielding 11 177 From the distribution of blood pressure values of the 100 sample men age 50 59 years in each sub category the *fraction* of each sub category with blood pressures above any particular value is immediately known We may calculate for example the number of cases of de novo coronary disease in each sub category with pressures above 110 mm Hg by multiplying this fraction by the number of cases in the category

Therefore we can estimate that there will be

of 100 cases in category 1	0 above 110 mm Hg
of 235 cases in category 2	0 above 110 mm Hg
of 277 cases in category 3	0 above 110 mm Hg
of 319 cases in category 4	0 above 110 mm Hg
of 423 cases in category 5	42 above 110 mm Hg
of 623 cases in category 6	0 above 110 mm Hg
of 931 cases in category 7	186 above 110 mm Hg
of 1308 cases in category 8	0 above 110 mm Hg
of 1865 cases in category 9	0 above 110 mm Hg
of 5096 cases in category 10	1019 above 110 mm Hg

The total number of de novo coronary disease cases with pressures above 110 mm Hg is 42 + 186 + 1019 or 1247 cases Therefore of the 11 177 de novo coronary disease cases in men 11 2% have pressures above 110 mm Hg Proceeding along similar lines for the women we can consider a time period long enough for 100 cases of de novo coronary disease to develop in

Chapter IX

THE RELATIONSHIP OF OVERWEIGHT WITH CORONARY HEART DISEASE

In today's medical practice there are few features more associated in the physician's mind with excessive cardiovascular disease in general and with coronary heart disease in particular than the phenomenon of overweight Indeed some physicians have interpreted essentially all the recent dietary work relating to coronary heart disease as being associated with caloric intake and the phenomenon of overweight While this latter view is incorrect it does underline the fact that overweight is high in the minds of physicians as a factor predisposing to cardiovascular disease It is therefore pertinent to determine precisely to what extent overweight is related to coronary heart disease and then to determine what mechanism may operate to make for an association between overweight and coronary heart disease assuming such association to exist This last point is most crucial for according to current day practice a large number of physicians feel that an overweight patient should reduce in *weight* in the effort to minimize his chances for development of future coronary heart disease This implies that simply being overweight is regarded by the physician as the factor which is responsible for any excessive risk of coronary heart disease It implies further more that there is nothing that can be done to delineate among the overweight individuals those who are especially prone to develop heart disease from those who may have even a lower risk of coronary heart disease than many underweight individuals Therefore mechanism by which overweight may become associated with coronary heart disease is an issue of paramount importance once the exact extent of the association is established

blood pressure would be expected to contribute a greater share of the risk of coronary disease in women than in men and therefore hypertension should be more prominent in women The mathematics formalizes this qualitative estimate

THE ROLE OF ESTROGENIC HORMONES

The large difference in coronary heart disease mortality rate among young women and young men and the finding of markedly lower lipoprotein levels in young women as compared with young men (a difference which decreases with increasing age) has naturally prompted great interest in the question of whether or not both the difference in disease incidence and in lipoprotein levels might be related to something about estrogenic hormone production in the female compared with the male The effects of estrogenic hormones upon serum lipoprotein levels have been and continue to be extensively studied Such studies do indeed indicate that pharmacologic estrogenic hormones can profoundly influence serum lipoprotein levels although they do not provide any evidence concerning physiologic estrogen production or handling as the basis for lipoprotein levels being different in men and women The pharmacologic effects of estrogens upon serum lipoproteins and Atherogenic Index will be discussed in detail in Chapter XV

The last question concerning differences in coronary heart disease incidence between men and women relates to the findings in diabetes mellitus Since this question is but part of the broader question of coronary heart disease in diabetes mellitus in general *this will be treated in Chapter XII*

Chapter IX

THE RELATIONSHIP OF OVERWEIGHT WITH CORONARY HEART DISEASE

IN TODAY'S medical practice there are few features more associated in the physician's mind with excessive cardiovascular disease in general and with coronary heart disease in particular than the phenomenon of overweight Indeed some physicians have interpreted essentially all the recent dietary work relating to coronary heart disease as being associated with caloric intake and the phenomenon of overweight While this latter view is incorrect it does underline the fact that overweight is high in the minds of physicians as a factor predisposing to cardio vascular disease It is therefore pertinent to determine precisely to what extent overweight is related to coronary heart disease and then to determine what mechanism may operate to make for an association between overweight and coronary heart disease assuming such association to exist This last point is most crucial for according to current day practice a large number of physicians feel that an overweight patient should reduce in *weight* in the effort to minimize his chances for development of future coronary heart disease This implies that simply *being* overweight is regarded by the physician as the factor which is responsible for any excessive risk of coronary heart disease It implies furthermore that there is nothing that can be done to delineate among the overweight individuals those who are especially prone to develop heart disease from those who may have even a *lower* risk of coronary heart disease than many underweight individuals Therefore mechanism by which overweight may become associated with coronary heart disease is an issue of paramount importance once the exact extent of the association is established

First of all it must be stated that the association between over weight and coronary heart disease is far from perfect Every physician who practices medicine realizes fully that many many patients with coronary heart disease are not overweight that patients develop coronary heart disease and die from it with weights considered within the normal or usual range and fur thermore that many patients develop coronary heart disease and die from it who are underweight by our usual height weight *standards Such considerations would still be correct even after* adjusting for such possibilities as difference in body frame and an incorrect appraisal of the exact amount of true adipose tissue in a particular patient With all such adjustments it would still be apparent that many people who are underweight or at normal weights can and do develop coronary heart disease Further more even though overweight may be a factor associated with excessive coronary heart disease many overweight patients remain so for many years without developing any signs and symptoms of coronary heart disease Where then does the evidence come from which *leads to so much emphasis on overweight* as a factor in degenerative vascular disease and in particular as a factor in the development of coronary heart disease? Probably the single most valid source of evidence on this subject is that which derives from the studies of life insurance policyholders These studies were in the nature of a follow up of insured policyholders at varying degrees of overweight and underweight from those who were markedly overweight to those who were well below the ideal weight for their height and build Such studies were reported by Dublin[4] the statistician for the Metropolitan Life Insurance Corporation Individuals were accepted for policies who were overweight but were rated upward in premium because of their status of overweight The exact analysis of Dublin s findings relating the coronary heart disease incidence rate in such policyholders to degree of overweight are presented in Table XXXI It is quite clear from the data presented there that among Dublin s insured policyholders who were 35% overweight the incidence of coronary heart disease was approximately 50% above that in the population of individuals who were at or below ideal weight This difference is large it is highly significant

and is essentially irrefutable To the author's knowledge no one has published any evidence which would contradict the findings of Dublin on these insured policyholders with respect to the excessive predisposition of appreciably overweight individuals to the development of fatal coronary heart disease Yet in a variety of ways some investigators have attempted to cast doubt upon this solidly established and highly significant information which has been published by Dublin concerning the relationship of overweight and coronary heart disease Many who have cast doubt upon this relationship have utilized studies of the extent of overweight in patients with already established clinical coronary heart disease in comparison with persons free of such manifest disease For example Certler and White[30] in their study of 97 men who developed myocardial infarction below the age of 40 years contrasted with a group of matched controls of the same age but without evidence of myocardial infarction were unimpressed with the difference in the degree of overweight of their myocardial infarction patients and their control series There is every reason to study the phenomenon of overweight in a series of patients with established clinical coronary heart disease such as survivors of myocardial infarction and to contrast the find

TABLE XXXI

MORTALITY FOR PERSONS RATED UP IN INSURANCE PREMIUMS FOR OVERWEIGHT

(Age group 20-64 years)

(from Dublin)

Departure from Average Weight (All classes overweight)	*Mortality (Expressed in % of Deaths Relative to Persons of Normal Weight)* MEN %	WOMEN %
Less than 30%	14?	139
30 39%	1 1	148
40 49%	1 8	1 6
0 59	31	1?5
60 4	99	145

For all classes of overweight Dublin reported coronary disease mortality = 149% of that for persons of average weight Also he points out that the distribution of causes of death is not appreciably different for the overweights than for the average weights Hence the table above can be regarded as representative of the relative coronary heart disease mortality rate among the various classes of overweight

ings in such a series with those in a series of individuals who have not developed clinical coronary heart disease In this text analogous data have been presented in previous chapters concerning lipoprotein findings However it has been pointed out carefully in previous discussions here that there are some major pitfalls that can deceive the unwary investigator in the use of such clinical material The crucial issue concerning overweight is the extent to which individuals who are overweight go on to develop clinical coronary heart disease *in the future* This is essentially the type of study for which Dublin has provided us with information On the other hand studies of clinical coronary heart disease already established in the form of survivorship of myocardial infarction are performed on a population of individuals who have not only developed clinical coronary heart disease but *who have been cared for by physicians* The extremely long history of medical suspicion of the unfavorable aspects of being overweight is such that overweight patients being treated for acute myocardial infarction are almost certain to lose weight during the period of hospitalization for the acute myocardial infarction Additionally many of them are encouraged to lose weight and do lose weight during the period of recovery from myocardial infarction A large number of such individuals will indicate upon questioning that their weight is considerably below the usual weight that had characterized them during the 5 10 15 or 20 years which had preceded their myocardial infarction On the other hand many such patients hardly know what their body weight had been before their myocardial infarction When asked whether they have altered their diet as a result of their myocardial infarction they will deny that they have, and yet when records are withdrawn detailing previous medical examinations insurance examinations or employment examinations it has been noted repeatedly that their post myocardial *infarction* weight is considerably below their pre myocardial infarction weight This is not to say that a certain number of patients may not gain weight after myocardial infarction as a result of the lesser physical activity allowed them in the course of their medical advice but one can be certain that the danger exists in the study of such clinical material as survivors of myocardial

infarction of an appreciable loss of weight in many patients Certainly one should be very wary of accepting data on the body weight of post myocardial infarction patients as being of real consequence with respect to the average degree of overweight in healthy individuals who will subsequently go on to develop myocardial infarction Undoubtedly Gertler and White were well aware of the possible biassing which this factor would have introduced into their study Hence while it is worthwhile knowing what their findings are reliance on such evidence to provide us with any evidence of a relationship between over weight and the incidence of myocardial infarction is hardly indi cated The same type of criticism should be levelled at a variety of other studies in the literature that have purported to show that the average survivor of myocardial infarction does not show any appreciable degree of overweight in comparison with the average person who has not experienced a myocardial infarc tion There does exist now in the literature another clear-cut study of the appropriate type concerning the relationship of over weight with development of clinical coronary heart disease that is heart disease occurring *after* the determination of the person s weight status It is only from such prospective studies of indi viduals whose weight is known in advance and who are subse quently followed that a valid determination can be made of the extent to which overweight predisposes to clinical coronary heart disease This latter study was conducted by the National Heart Institute of the United States Public Health Service in the com munity of Framingham Massachusetts as part of a long term survey of the development of cardiovascular disease and other diseases in individuals of a reasonably representative community in the United States These data have been recently published[23] In that study 52 acceptable documented cases of arteriosclerotic heart disease were observed to develop over a 4 year period out of a population sample of 898 men who had undergone com plete physical examinations Analyses of the data showed clearly that the attack rate of coronary heart disease was appreciably and significantly greater during the four year follow up period for the overweight men than for otherwise comparable but not

ings in such a series with those in a series of individuals who have not developed clinical coronary heart disease In this text analogous data have been presented in previous chapters concerning lipoprotein findings However, it has been pointed out carefully in previous discussions here that there are some major pitfalls that can deceive the unwary investigator in the use of such clinical material The crucial issue concerning overweight is the extent to which individuals who are overweight go on to develop clinical coronary heart disease *in the future* This is essentially the type of study for which Dublin has provided us with information On the other hand studies of clinical coronary heart disease already established in the form of survivorship of myocardial infarction are performed on a population of individuals who have not only developed clinical coronary heart disease but *who have been cared for by physicians* The extremely long history of medical suspicion of the unfavorable aspects of being overweight is such that overweight patients being treated for acute myocardial infarction are almost certain to lose weight during the period of hospitalization for the acute myocardial infarction Additionally many of them are encouraged to lose weight and do lose weight during the period of recovery from myocardial infarction A large number of such individuals will indicate upon questioning that their weight is considerably below the usual weight that had characterized them during the 5 10 15 or 20 years which had preceded their myocardial infarction On the other hand many such patients hardly know what their body weight had been before their myocardial infarction When asked whether they have altered their diet as a result of their myocardial infarction they will deny that they have and yet when records are withdrawn detailing previous medical examinations insurance examinations or employment examinations it has been noted repeatedly that their post myocardial infarction weight is considerably below their pre myocardial infarction weight This is not to say that a certain number of patients may not gain weight after myocardial infarction as a result of the lesser physical activity allowed them in the course of their medical advice but one can be certain that the danger exists in the study of such clinical material as survivors of myocardial

relationship either of blood lipoproteins or blood pressure with overweight might increase the hazard of overweight persons of developing future clinical coronary heart disease it would be pertinent to know whether there is or is not there is still left over any extra hazard of coronary heart disease in overweight persons If there is *no* extra hazard left over to be accounted for the notion that the phenomenon of overweight per se increases the hazard of coronary disease could be dispelled If there is an extra hazard left over it is urgent to learn the nature of its possible basis

OVERWEIGHT, LIPOPROTEIN LEVELS, AND ATHEROGENIC INDEX VALUES

The evidence discussed above clearly implicates overweight as a factor producing an excessive risk of clinical coronary heart disease and hence correspondingly an excessive rate of development of sub-clinical coronary heart disease The extent to which this effect of overweight can be explained by any possible association of overweight with the blood level of the four important lipoprotein classes (S_f0 12 S_f12 20 S_f20 100 and S_f100-400) and with the derived value the Atherogenic Index must be understood Population samples are available for whom the blood lipoproteins height and weight have been measured as a routine part of periodic employment examinations so that a reasonable cross section of individuals of both sexes and at various ages is available for study of this issue The measured values of the various lipoprotein classes and of the combined value which summarizes the information with respect to coronary heart disease namely the Atherogenic Index are listed for various degrees of overweight in Table XXXII In these tabulations degree of overweight or underweight is expressed in terms of the value known as the relative weight of an individual The definition of relative weight as used here is the person s actual body weight divided by the ideal body weight utilizing the Metropolitan Life Insurance Height and Weight Tables to determine ideal weight Thus if an individual is characterized by relative weight of 1 20 it is meant that his weight is 20% above

overweight men The actual findings reported by Dawber and co workers in the Framingham Study were as follows

Weight Category	Attack Rate of Arteriosclerotic Heart Disease in New Cases Per 1000 at Risk (4 year period)
20% or more above median weight	123 cases per 1000
13 to 19% above median weight	105 cases per 1000
0 to 12% above median weight	60 cases per 1000
Below median weight	40 cases per 1000

The evidence derived from this study indicates an association of overweight with heart disease risk of approximately the same order of magnitude as that previously published by Dublin *There existed every reason to expect that these data would confirm* Dublin s data and they do In the face of such strong evidence from both the study of Dublin on the insured overweights and the data of the Framingham Heart Project there would appear less reason than ever to question the positive relationship of overweight with the subsequent development of clinical coronary heart disease Rather the strong evidence should make even more suspect conclusions concerning overweight derived from the study of myocardial infarction survivors

With the clear cut establishment of an association of over weight with excessive coronary heart disease risk several ques tions come to the fore First the evidence derived in previous chapters demonstrated two major features characterize individ uals in terms of their subsequent risk of clinical coronary heart disease These are (1) their blood lipoprotein levels and athero genic index values and (2) their habitual blood pressures It is pertinent first to determine the extent to which overweight *may influence either of these two factors* For if either the lipo protein level and atherogenic index value are elevated on the average in overweight individuals or if the blood pressure is elevated on the average in overweight individuals there would exist a well defined basis for the expectation of a positive asso ciation between overweight and the hazard of clinical coronary heart disease Of even greater importance some insight into the mechanism by which such association arises would be avail able Once an estimate were available of the extent to which a

the ideal weight listed by the Metropolitan Height and Weight Tables No need exists to claim that the ideal values listed in the Metropolitan Life Insurance Tables are truly ideal weights They do serve as a set of useful reference points and any findings based upon their use would hardly be altered in any significant manner by any other choice of reference weights

All four lipoprotein classes (sf-12 12 20 20 100 and 100 400) and the Atherogenic Index show appreciable rises in average value upon comparison of the significantly underweight individuals with those appreciably overweight with a fairly smooth rising trend for the intermediary weight groups Inspection of the table for various individual lipoprotein classes reveals that the effect of overweight is more strikingly associated with elevation of the sf20 100 and sf100-400 lipoproteins than it is with elevation of the sf0 12 and sf12 20 lipoproteins At the outset it must be stressed that these variations in lipoprotein levels and Atherogenic Index values with degree of overweight are *average* findings for the group of individuals in each particular relative weight range In any particular relative weight range individuals are found who have low moderate or even quite high Atherogenic Index values although there will be a higher frequency of high values of the Atherogenic Index with a higher degree of overweight than with a moderate degree of overweight and correspondingly a higher frequency of high values with a moderate degree of overweight than for groups markedly below ideal weight Similarly there exists a higher frequency of low values in individuals who are underweight or at ideal weight in comparison with those who are appreciably overweight These findings all occur because the correlation between relative weight and Atherogenic Index is far from perfect even though it is clear-cut and definite This point is summarized in Table XXXIII which gives the frequency of various Atherogenic Index values at various degrees of overweight and underweight in a study group of 834 men in the 30 39 year age category The entire group of men is then divided into four sub-groups those 10% or more underweight those between 10% underweight and 10% overweight and those 10 to 20% overweight and those 30% or more overweight (all on the relative weight scale) In each

TABLE XXXII

RELATIONSHIP OF DEGREE OF OVERWEIGHT WITH BLOOD LIPOPROTEIN LEVELS AND ATHEROGENIC INDEX VALUES

(Based upon study of 834 consecutive 30 39 year old men)*

Relative Weight Group	*Number of Cases*	Mean Lipoprotein Level (mg/100ml) $S_f 0$ 12	$S_f 12$ 20	$S_f 20$ 100	$S_f 100$ 400	*Mean Atherogenic Index (units)*
Less than 0 80 (Mean = 0 76)	11	347 2	56 9	78 6	36 3	61 9
0 80 0 89 (Mean = 0 86)	86	337 8	41 4	70 1	33 2	59 1
0 90 0 99 (Mean = 0 9[illegible])	219	319 2	48 2	83 1	38 5	61 6
1 00 1 09 (Mean = 1 0[illegible])	219	355 3	51 3	91 6	48 8	69 1
1 10 1 19 (Mean = 1 11)	168	367 1	5[illegible] 3	100 4	61 1	75 2
1 20 1 29 (Mean = 1 [illegible]3)	7[illegible]	360 9	[illegible]1 9	112 9	78 4	79 1
1 30 or higher (Mean = 1 37)	[illegible]6	3[illegible]9 2	[illegible] 3	116 0	86 7	82 0

*All men were employees at one industrial installation Examinations were part of periodic medical examinations

coronary heart disease for individuals of several ages at various Atherogenic Index values Thus if illustrative considerations are limited to 30 39 year old males those tabulations will allow a ranking of individuals upon the Atherogenic Index values and a direct calculation of the relative incidence rate of clinical coronary heart disease at one Atherogenic Index value for comparison with the incidence rate at any other Atherogenic Index value The data of Table XXXII indicate that for 30 39 year old males the individual who is 35% overweight will show an average Atherogenic Index value of approximately 82 units whereas the individual who is at ideal weight will show an average Atherogenic Index value of 67 units From Table XV for the value of 82 Atherogenic Index units (in those individuals 35% overweight) the risk of coronary heart disease would be 7 0 times the reference value of 30 A I units and for individuals at ideal weight whose Atherogenic Index value is 67 units the risk of coronary heart disease would be 3 4 times the reference value Therefore the relative risk or rate of mortality from coronary heart disease for these two groups would be the first value divided by the second or a 7 0 over 3 4 = 2 1 fold increase in attack rate for the overweight group compared with the ideal weight group The first approximation has been obtained by calculating the risk of coronary heart disease for the average person who is 35% overweight Therefore Atherogenic Index elevation in overweight persons leads to a prediction of excessive coronary heart disease mortality between the published values of Dublin and of Dawber However overall coronary disease risk requires evaluation of the contribution from the blood pressure as well as from the Atherogenic Index

RELATIONSHIP OF OVERWEIGHT, BLOOD PRESSURE, AND CORONARY HEART DISEASE

The evaluation of a feature such as overweight in relation to excessive coronary heart disease would be incomplete without an analysis of the extent to which overweight may affect blood pressure and to which this may alter coronary heart disease incidence rate There have been numerous studies of the relation

TABLE XXXIII

DISTRIBUTION OF ATHEROGENIC INDEX VALUES IN THE VARIOUS RELATIVE WEIGHT CATEGORIES

(30-39 year old men)

Relative Weight Category	*Atherogenic Index Values* Low Less than 60 (units)	Moderate 60-89 (units)	Elevated 90-109 (units)	Markedly Elevated 110 or higher (units)
Less than 0.90	53.8%	41.2%	1.7%	3.4%
0.90-1.09	38.9%	45.4%	10.6%	5.0%
1.10-1.29	26.0%	51.1%	12.7%	10.2%
Greater than 1.30	26.4%	38.2%	20.6%	14.7%

such category the fraction of the group with markedly elevated, elevated, moderate, and low Atherogenic Index values are presented. It is seen that any value of the Atherogenic Index *can* occur in any of the relative weight categories but clearly the high values are *more frequent* in the overweight groups than in the other groups. Correspondingly low Atherogenic Index values are more frequent in the underweight groups than in the other weight categories.

EXTENT TO WHICH THE ATHEROGENIC INDEX ELEVATION IN OVERWEIGHT INDIVIDUALS ACCOUNTS FOR THEIR INCREASED CORONARY HEART DISEASE MORTALITY

Dublin's data on insured overweights demonstrated that the 35% overweight individual shows approximately a 1.5 fold mortality from diseases of the coronary arteries compared with the individual who is at ideal weight. Dawber's Framingham data indicate approximately a 3 fold mortality for the same degree of overweight. In the effort to understand the mechanism for this observed increase in mortality, the extent to which the effect of overweight on factors known to be associated with coronary heart disease might be expected to alter the mortality from coronary heart disease must be determined. In Chapter V were presented the tabulations which give the incidence rate for clinical

is given the relative risk (of coronary heart disease or coronary heart disease incidence rate) for various diastolic blood pressure values For a diastolic pressure of 78 7 mm Hg the coronary heart disease risk is 3 9 For a diastolic pressure of 74 7 mm Hg the coronary heart disease risk is 3 2 Therefore the relative coronary heart disease rate for the average person 35% over weight (whose mean pressure is 78 7 mm Hg) is 1 2 fold that of the average person at ideal weight (whose mean pressure is 74 7 mm Hg) This is the extent to which the degree of over weight increases coronary heart disease risk via the association of the former with the diastolic blood pressure

THE COMBINED EFFECT OF ATHEROGENIC INDEX AND BLOOD PRESSURE ELEVATION IN INCREASED RISK OF CORONARY HEART DISEASE IN OVERWEIGHT PERSONS

It was demonstrated earlier (see Chapter V) that the Atherogenic Index and the diastolic blood pressure are independent factors operating to determine the risk of coronary heart disease in any individual Further it was shown that the best approximation to the overall risk of coronary heart disease *from these* two independent factors can be estimated by multiplication of the coronary disease risk factor for the Atherogenic Index effect by that for the diastolic blood pressure In this case for the comparison of the average person who is 35% overweight with the average person at ideal weight the Atherogenic Index increases the coronary heart disease risk 2 1 fold and the diastolic blood pressure increases that risk 1 2 fold The combined effect of both factors therefore predicts a 2 1x1 2 or 2 5 fold coronary heart disease risk (or incidence rate) for the 35% overweight individual This lies between the 1 5 fold risk reported by Dublin and the 3 fold risk reported by Dawber Certainly it would appear that the major effect of overweight in production of an increase in coronary heart disease risk is explainable through the combination of its effects upon the Atherogenic Index and the diastolic blood pressure There may well exist no excessive risk

The average of the pressure recorded by the physician (non reclining) and that taken by the nurse (after 10 minute rest) is used here

ship between overweight and blood pressure[43 44 45] The measured relationship between blood pressure and relative weights for the 30 39 year old men described above is presented in Table XXXIV The regular progression of increasing average diastolic blood pressure with increasing average degree of overweight is apparent in the data of all investigators Again as with the Atherogenic Index the finding of increase in diastolic blood pressure with increase in weight is an *average* trend Therefore, at low relative weight average weight or at a marked degree of over weight, the diastolic blood pressure can be low moderate or high But unmistakably there is an increasing frequency of high values of the diastolic blood pressure with increasing relative weight From the data of Table XXXIV, the average diastolic blood pressure for 30 39 year old males 35% overweight is 78 7 mm Hg* in contrast with a pressure of 74 7 mm Hg for persons of the same age group who are at ideal weight In Table XIV

TABLE XXXIV

RELATIONSHIP OF DEGREE OF OVERWEIGHT WITH DIASTOLIC BLOOD PRESSURE

(Based upon study of 834 consecutive 30 39 year old men)

Relative Weight Group	*Number of Cases*	*Mean Diastolic Blood Pressure (mm Hg)* NURSE*	PHYSICIAN*
Less than 0 80 (Mean = 0 76)	11	68 0	75.8
0 80 0 89 (Mean = 0 86)	86	69 1	76.9
0 90 0 99 (Mean = 0 95)	219	70 7	79.2
1 00 1 09 (Mean = 1 05)	249	69.5	79 1
1 10 1 19 (Mean = 1 14)	168	70.2	82 1
1.20 1.29 (Mean = 1.25)	75	71 1	84 6
1.30 or higher (Mean = 1 37)	26	71 8	85 9

* These blood pressures were taken by a nurse after 10 minutes of rest by the subject

* These pressures were taken by the physician during the course of the physical examination which preceded the rest period

is given the relative risk (of coronary heart disease or coronary heart disease incidence rate) for various diastolic blood pressure values. For a diastolic pressure of 78.7 mm Hg the coronary heart disease risk is 3.9. For a diastolic pressure of 74.7 mm Hg the coronary heart disease risk is 3.2. Therefore the relative coronary heart disease rate for the average person 30% over weight (whose mean pressure is 78.7 mm Hg) is 1.2 fold that of the average person at ideal weight (whose mean pressure is 74.7 mm Hg). This is the extent to which the degree of over weight increases coronary heart disease risk via the association of the former with the diastolic blood pressure.

THE COMBINED EFFECT OF ATHEROGENIC INDEX AND BLOOD PRESSURE ELEVATION IN INCREASED RISK OF CORONARY HEART DISEASE IN OVERWEIGHT PERSONS

It was demonstrated earlier (see Chapter V) that the Atherogenic Index and the diastolic blood pressure are independent factors operating to determine the risk of coronary heart disease in any individual. Further, it was shown that the best approximation to the overall risk of coronary heart disease from these two independent factors can be estimated by multiplication of the coronary disease risk factor for the Atherogenic Index effect by that for the diastolic blood pressure. In this case, for the comparison of the average person who is 35% overweight with the average person at ideal weight the Atherogenic Index increases the coronary heart disease risk 2.1 fold and the diastolic blood pressure increases that risk 1.2 fold. The combined effect of both factors therefore predicts a 2.1x1.2 or 2.5 fold coronary heart disease risk (or incidence rate) for the 35% overweight individual. This lies between the 1.5 fold risk reported by Dublin and the 3 fold risk reported by Dawber. Certainly it would appear that the major effect of overweight in production of an increase in coronary heart disease risk is explainable through the combination of its effects upon the Atherogenic Index and the diastolic blood pressure. There may well exist no excessive risk

*The average of the pressure recorded by the physician (non reclining) and that taken by the nurse (after 10 minute rest) is used here.

left over to be accounted for by *overweight per se* Indeed there never did exist any direct evidence to indicate that load or strain upon the heart due to the phenomenon of overweight *per se* is in any way related to an increased risk of coronary heart disease The semi popular excess baggage concept of the effect of overweight upon the heart at least with respect to coronary heart disease finds no support from these data nor from any other scientific data

THE PRACTICAL CLINICAL IMPLICATIONS OF THE MECHANISMS BY WHICH OVERWEIGHT INCREASES CORONARY HEART DISEASE RISK

That at least the major share of the effect of overweight in increasing the risk of coronary heart disease operates via the Atherogenic Index and blood pressure effects is hardly a matter of academic importance alone Clinically, physicians have in general warned the overweight patient that his risk of coronary heart disease is increased by his status of being overweight In an overall sense this has been completely correct However now that at least the largest part of the mechanism by which overweight operates to produce an excessive coronary heart disease risk is understood such a clinical approach is definitely outmoded For if an overweight person is one of the many who have escaped the effect of overweight upon Atherogenic Index and blood pressure level then there exists no justification for assignment of an excessive coronary disease risk to that patient Instead such a patient can be re assured that he does not share the *average* increase in coronary heart disease risk experienced by the overweight group It follows also that *some* overweight persons must experience a much greater than average effect of overweight upon either the Atherogenic Index or the diastolic blood pressure or both Such persons are subject to a much greater increase in coronary heart disease risk as a direct result of their being overweight *than is the case for the average* person overweight to the same extent It becomes apparent then that clinically much more can be done to assess the true significance of overweight in a particular patient when the blood

pressure and lipoprotein Atherogenic Index measurements are available to the physician

THE EFFECT OF CORRECTION OF OVERWEIGHT UPON ATHEROGENIC INDEX AND BLOOD PRESSURE VALUES

An important question arises in the mind of the clinician whenever a relationship between two physiological or biochemical variables has been demonstrated to exist That question is If one of the variables is changed in a favorable direction will the other variable also change in a favorable direction? This is certainly a valid question for it is possible for two variables to be correlated and yet to have one such variable uninfluenced when a *change* occurs in the other of the pair In the present case the problem centers around whether or not lipoprotein Atherogenic Index values and blood pressure values will fall if overweight is corrected It is possible to conceive that some hypothetical third factor controls the degree of overweight and separately controls the Atherogenic Index value The observed correlation between overweight and Atherogenic Index value could under these circumstances be the result of a correlation of both of them with the hypothetical third factor It can be imagined that correction of overweight might fail to alter the hypothetical third factor and hence fail to alter the Atherogenic Index value Clearly such speculation should well be replaced by a direct determination of what happens to lipoprotein Atherogenic Index values and blood pressure when body weight is altered both in the direction of an increase and a decrease

There exist two ways of obtaining direct experimental answers to these questions in human subjects One method involves the specific experiment of having a group of subjects diet to reduce in weight with observation serially of Atherogenic Index and blood pressure changes The other approach involves what may be properly regarded as a natural experiment in which individuals are observed over a period of years without any specific medical advice Of their own choice some will eat more others the same and still others less Some will increase their physical activity otheres will not change such activity and

some will decrease their physical activity The net result will be that some will increase in weight others will remain unchanged and still others will lose weight in such a natural experiment The changes in a variable such as Atherogenic Index can readily be ascertained if such a group of persons is periodically checked as part of a routine examination without any knowledge of the nature of the experiment Extensive data are now available for both types of experimental approach to the question of the effect of change in weight Of the two types of data, those derived from the natural experiment are in many ways far more satisfactory to the physician in practise His real interest lies in knowing what happens to persons altering their weights under the usual circumstances of living Such natural experiments involve less of the drastic unphysiologic and unusual type of dietary regimen and hence provide information more representative of the dietary patterns persons are likely to adhere to over long periods of time

The data for such a natural experiment were obtained from serial blood studies of 374 men who were examined on two occa sions one to three years apart in routine employment medical examinations Weight and lipoprotein levels were determined on both occasions although none of the persons examined had any idea that such studies were in progress Therefore it is hardly con ceivable that factors such as an effort to lose weight rapidly before a medical visit could have operated to any significant extent in these studies The subjects were considered on the basis of whether they had lost 5 or more pounds from the first to the second examination lost 0 to 5 pounds experienced no change had gained 0 to 5 pounds or had gained more than 5 pounds Lipoproteins of the sf0 12 12 20 20 100 and 100-400 classes plus the derived Atherogenic Index values were measured for all groups of subjects The average changes for the several groups are presented in Table XXXV It is clear from those data that the lipoproteins and Atherogenic Index values rise appreciably with increase in weight between the two examinations and that they fall appreciably for those men who decrease in weight between the two examinations This settles definitively the ques tion concerning whether weight alteration does alter lipoproteins

TABLE XXV

EFFECT OF WEIGHT ALTERATION ON SERUM LIPOPROTEIN LEVELS AND ATHEROGENIC INDEX VALUES

(Natural Life [illegible] 374 Subjects)

	Number of Subjects	Mean S_f 0-12	Mean S_f 12-20	Mean S_f 20-100	Mean S_f 100-400	Mean A.I.	Body Weight (pounds)
Persons Losing 5 or More Pounds Between Examinations							
1st Examination	73	[illegible]	50.6	[illegible]	[illegible]	71.9	180.6
2nd Examination	73	[illegible]	46.8	86.3	[illegible]	64.6	169.9
Change		− 18.1	− 3.8	[illegible]	[illegible]	− 7.3	− 10.7
Persons Losing 0 to 5 Pounds Between Examinations							
1st Examination	77	[illegible]	47.9	[illegible]	[illegible]	70.0	169.7
2nd Examination	77	358.4	[illegible]	91.8	53.8	[illegible]	[illegible]
Change		− 11.1	[illegible]	+ 7.6	[illegible]	− 0.3	[illegible]
Persons Who Did Not Change in Weight Between Examinations							
1st Examination	37	350.3	11.1	[illegible]	[illegible]	63.9	[illegible]
2nd Examination	[illegible]	[illegible]	11.3	[illegible]	[illegible]	61.3	163.6
Change		− 7.7	+ 0.2	[illegible]	[illegible]	+ 0.4	0
Persons Who Gained 0 to 5 Pounds Between Examinations							
1st Examination	81	345.2	46.3	81.7	43.4	[illegible]	161.9
2nd Examination	81	[illegible]	50.0	96.6	[illegible]	72.1	164.3
Change		+ 6.9	+ 3.7	[illegible]	+ 17.1	[illegible]	+ 2.4
Persons Who Gained 5 or More Pounds Between Examinations							
1st Examination	103	[illegible]	52.2	93.2	49.3	69.5	162.3
2nd Examination	103	360.7	[illegible]	110.8	68.5	[illegible]	171.9
Change		+ 5.0	+ 4.0	+ 17.6	+ 19.2	+ 8.1	+ 9.6

some will decrease their physical activity The net result will be that some will increase in weight others will remain unchanged, and still others will lose weight in such a natural experiment The changes in a variable such as Atherogenic Index can readily be ascertained if such a group of persons is periodically checked as part of a routine examination without any knowledge of the nature of the experiment Extensive data are now available for both types of experimental approach to the question of the effect of change in weight Of the two types of data those derived from the natural experiment are in many ways far more satisfactory to the physician in practise His real interest lies in knowing what happens to persons altering their weights under the usual circumstances of living Such natural experiments involve less of the drastic unphysiologic and unusual type of dietary regimen and hence provide information more representative of the dietary patterns persons are likely to adhere to over long periods of time

The data for such a natural experiment were obtained from serial blood studies of 374 men who were examined on two occasions one to three years apart in routine employment medical examinations Weight and lipoprotein levels were determined on both occasions although none of the persons examined had any idea that such studies were in progress Therefore it is hardly conceivable that factors such as an effort to lose weight rapidly before a medical visit could have operated to any significant extent in these studies The subjects were considered on the basis of whether they had lost 5 or more pounds from the first to the second examination lost 0 to 5 pounds experienced no change had gained 0 to 5 pounds or had gained more than 5 pounds Lipoproteins of the S_f0 12 12 20 20 100 and 100-400 classes plus the derived Atherogenic Index values were measured for all groups of subjects The average changes for the several groups are presented in Table XXXV It is clear from those data that the lipoproteins and Atherogenic Index values rise appreciably with increase in weight between the two examinations and that they fall appreciably for those men who decrease in weight between the two examinations This settles definitively the question concerning whether weight alteration does alter lipoproteins

TABLE XXV

EFFECT OF [illegible] ALTERATIONS ON SERUM LIPOPROTEIN LEVELS AND ATHEROGENIC INDEX VALUES

([illegible] Subjects)

	Number of Subjects	Mean S_f 0-12	Mean S_f [illegible]	Mean S_f [illegible]-100	Mean S_f 100-400	Mean A.I.	Body Weight (pounds)
Persons [illegible] Between [illegible]							
1st Examination	73	[illegible]	50.6	[illegible]	[illegible]	71.9	180.6
2nd Examination	73	[illegible]	46.8	86.3	[illegible]	64.6	169.9
Change		− 18.1	− 3.8	[illegible]	[illegible]	− 7.3	− 10.7
Persons Losing 0 to 5 Pounds Between Examinations							
1st Examination	[illegible]	369.5	47.9	[illegible]	[illegible]	70.0	169.7
2nd Examination	[illegible]	358.4	50.7	91.8	53.8	[illegible]	[illegible]
Change		− 11.1	+ [illegible]	+ 7.6	[illegible]	− 0.3	− 2.1
Persons Who Did Not Change in Weight Between Examinations							
1st Examination	37	350.3	41.1	81.1	[illegible]	[illegible]	[illegible]
2nd Examination	37	[illegible]	41.3	81	[illegible]	61.3	163.6
Change		− 7.7	+ 0.2	[illegible]	[illegible]	+ 0.4	0
Persons Who Gained 0 to 5 Pounds Between [illegible]							
1st Examination	84	345.2	46.3	81.7	43.1	[illegible]	161.9
2nd Examination	84	[illegible]	50.0	96.6	60	[illegible]	164.3
Change		+ 6.9	+ 3.7	[illegible]	+ 17.1	[illegible]	+ 2.4
Persons Who Gained 5 or More Pounds Between Examinations							
1st Examination	103	[illegible]	[illegible]	93.2	49.3	69.5	162.3
2nd Examination	103	360.7	62.2	110.8	68.5	[illegible]	171.9
Change		+ 5.0	+ 4.0	[illegible]	+ 19.2	[illegible]	+ 9.6

and Atherogenic Index values in the expected direction The fact that lipoproteins and Atherogenic Index values *are* altered in the expected direction removes any need for a hypothetical third factor which controls body weight and lipoproteins independently From the clinical point of view weight reduction can be counted on to reduce lipoprotein Atherogenic Index values a favorable trend, whereas weight gain will result in a rise in Atherogenic Index values a highly unfavorable trend

The findings from the above described natural experiment are supported by relatively short term experiments in overweight persons who were induced to lose weight on a prescribed 1000 calorie reduction diet low in animal fat and in carbohydrate[46] Twenty eight women all significantly overweight participated in a weight reduction program over a two month period The lipoprotein and Atherogenic Index changes in this study are presented in Table XXXVI Appreciable falls in all four classes of lipoproteins (S_f0 12 12 20 20 100 and 100-400) and in the Ath*erogenic Index values accompanied the weight loss which* averaged 14 pounds for the overall group of 28 women The probable mechanism by which weight reduction results in lipoprotein lowering and weight gain in lipoprotein elevation are to be discussed in detail in Chapter X The pertinent issue here is that both in short term medical studies and in long term natural experiments weight alterations are paralleled by lipoprotein and Atherogenic Index alterations

CHANGES IN DIASTOLIC BLOOD PRESSURE WITH CHANGE IN WEIGHT

Precisely the same type of question arises with respect to the relationship of diastolic blood pressure to degree of over weight as arose for the Atherogenic Index overweight *relationship* Will correction of overweight result in a fall in the average diastolic blood pressure? The work of numerous investigators has established satisfactorily[47 48 49 50 51] that correction of over weight is attended by a fall both in systolic and diastolic blood pressures and that such reductions occur both in originally normotensive and hypertensive persons

TABLE XXXVI

EFFECT OF SHORT TERM MEDICAL WEIGHT REDUCTION PROGRAM OF SERUM LIPOPROTEIN LEVELS AND ATHEROGENIC INDEX VALUES

(1000 calorie diet in 8 Female subjects)

	S_f 0 1? mg/100 ml	S_f1? ?0 mg/100ml	S_f?0 100 mg/100ml	S_f100 400 mg/100ml	Atherogenic Index	Body Weight (pounds)
Initial Mean Values	372	93	91	61	81	212
Mean Values after ? Months on Diet	3[illegible]6	61	[illegible]	27	61	198
Changes	− 46	− 3[illegible]	− [illegible]2	− 37	− 20	− 14

EFFECT OF CORRECTION OF OVERWEIGHT UPON CORONARY HEART DISEASE MORTALITY

Both major factors known to be associated with increase in the risk of coronary heart disease mortality the Atherogenic Index value and the diastolic blood pressure are positively associated with the degree of overweight Indeed these two factors together account for essentially all of the known effect of overweight in increasing the incidence rate or risk of coronary heart disease Further excellent evidence is available that correction of overweight will on the average alter the blood pressure factor and the Atherogenic Index in a favorable direction This would lead to the expectation that correction of overweight *should lead to a reduction in the incidence rate or risk of coronary heart disease* There already exists cogent direct evidence *to indicate that correction of overweight does indeed reduce the* risk of fatal coronary heart disease Dublin and Marks of the Metropolitan Life Insurance Company have reported on the mortality experience of persons originally rated up in insurance premiums because of overweight but who subsequently received lower ratings after reduction in weight This mortality experience was compared with that for the overall group of persons originally rated up in insurance premium for overweight For their entire group of cases they found for intermediate degrees of overweight a 42% increase in mortality in comparison with persons not rated up in premium whereas for the group originally rated up but later rerated because of loss of weight the increase in mortality was only 13% This is a marked reduction in mortality and it is not even possible to prove that the 13% increase that remained was real For the extreme overweights they found a 79% increase in mortality for the overall group rated up but for those who were re rated because of loss in weight the increased mortality was only 9% which again cannot definitely be proven to be a real increase Unquestionably this evidence shows that overweight correction does reduce mortality risk Since coronary heart disease is a major contributor to the excessive mortality observed it is certain that this particular source of mortality was reduced Thus not only do all the logical ele

ments point to the expectation that correction of overweight will reduce the risk of coronary heart disease mortality but the direct field test provides convincing evidence that this expectation is realized

Chapter X

DIET AND CORONARY HEART DISEASE

No SUBJECT has been more in the limelight of possible approaches to coronary heart disease prevention and treatment than that concerning diet From numerous sources and from a variety of types of information have come the suggestion that the diet which people habitually consume may in some way be related to their risk of premature coronary heart disease It will be necessary to consider the validity of evidence concerning possible relationships between diet and coronary heart disease so as to facilitate the physician s decision concerning the practical application of diet in the prevention of coronary heart disease Prominent among the types of evidence which bear upon this question have been those which associate a high incidence rate of coronary heart disease with prosperity in a country adequate to allow for abundant consumption of certain kinds of foods Thus the Bantus of South Africa, the Okinawans the Chinese and the Japanese (at least during some era) have all been quoted to have a low incidence rate of coronary heart disease whereas the population of countries of much greater prosperity and a higher food intake not only of fat but also of calories in general, have been quoted to show a higher incidence rate of coronary heart disease As evidence that deserves careful perusal such evidence is extremely valuable for it may provide some major leads toward understanding of coronary heart disease However among other criticisms one criticism has been semi justifiably levelled at such evidence in a serious way That criticism has essentially stated the following If any two of the population groups quoted as having grossly different coronary disease death rates and grossly different diets are compared it is found that a

wide variety of features can also be used to differentiate these populations beside that of diet

First it has been pointed out that the differences in climate and other aspects of the environment for the persons in one country as compared with those for persons in another country are as large or larger than the differences in habitual dietary intake of certain foods Second there are ethnic differences between the peoples of the various countries involved that might conceivably be associated with alterations as important as or more important than the difference in food intake Third there are gross differences in major occupational activities for the individuals in some of these areas versus those in other areas Occupation has on other grounds been singled out as a factor involved in the development of coronary heart disease (see Chapter XIV) Fourth those who feel that stress of living is important have pointed out that various aspects of the complex circumstances of living are such that stresses may be quite different in one geographic area from another Still other possible differences between persons residing in one area and another could be mentioned over and above any differences in diet that are known to exist To some extent various of these criticisms can be countered and have been countered by investigators interested in epidemiologic investigation For example the issue of geography climate and other environmental conditions as being perhaps of more importance than diet is in large measure contradicted by several sets of observations First Collumbine[55] has pointed out that the native Ceylonese in Ceylon show a low incidence rate of clinical coronary heart disease and subsist upon a low intake of dietary fat

On the other hand the Dutch burghers who reside in Ceylon have a much higher incidence of clinical coronary heart disease an incidence not very different from that which characterizes their cohorts in Holland If it were climatic or geographic conditions per se that were important in lowering the overall rate of coronary heart disease in Ceylon there would be every reason to expect that the Dutch burghers would show to some extent at least the same protection that the Ceylonese are afforded If the factors of climate and geography were paramount the Dutch

burghers of Ceylon would be expected to show the same coronary disease attack rate as do the native Ceylonese That they do not show the same rate is strong evidence that some factor other than geography *climate or other aspects of the environment* must be much more crucial in determining the coronary heart disease incidence rate Similarly evidence has been adduced by Bronte Stewart and co workers[3-4] that the coronary disease incidence rate in South Africa is much higher for the South African whites than it is for the Bantus in that area Again if geography, climatic conditions or similar environmental factors were paramount it would be anticipated that the whites in South Africa would not fare so much more poorly than the Bantus with respect to the development of clinical coronary heart disease

Analogous evidence bearing upon this same issue has been developed by others For example Larsen [5] has shown that Japanese residing in Western Countries experience a coronary disease incidence rate more nearly comparable with that of whites in such countries than they do with that of Japanese in Japan If the ethnic factor were of paramount importance one would anticipate that the Japanese who have migrated to the Western Countries should still show the protection that the ethnic factor *provides which they apparently do not show This type of evi* dence would counter another of the explanations alternative to diet which have been proposed for the difference in geographic incidence of coronary heart disease

When all these considerations are weighed pro and con we are still left with the conclusion that the epidemiologic incidence concerning the relationship of coronary heart disease with the diet is of itself not definitive That it produces valuable clues for direct experimental and clinical investigation is *not* denied even by those who are most vehemently opposed to acceptance of epidemiologic evidence that habitual diet is a factor in explaining the differences in coronary disease incidence rate in different countries What is really of concern to the physician dealing with the problem of coronary heart disease in the United States is a knowledge *of what role the dietary usually* consumed by persons in the United States plays in the development of clin

ical coronary heart disease Further his problem centers about what might be done by dietary means to alter the outlook for the development of coronary heart disease in individuals in this country by dietary alteration Therefore what is needed is evidence of a controlled character derived in typical individuals in the United States concerning the effect of dietary factors upon the evolution of clinical coronary heart disease and of the effect of alteration of such dietary factors under the practical circumstances which might be considered feasible in the usual pattern of living There are two major approaches that can be applied scientifically to this question Our interest truly lies in the evolution of serious clinical manifestations of coronary heart disease Therefore the effect of diet can be studied directly with respect to the rate of development of clinical coronary heart disease A comparison of diets in large sub-groups of the population could be made with subsequent followup of such sub groups in the population for an adequate period of time to determine the incidence rate of coronary heart disease in relationship to the type and quantity of the various foodstuffs habitually consumed by the various sub-groups Such studies are by no means simple

In a country like the United States there exists considerable heterogeneity in the population heterogeneity in occupational distribution heterogeneity with respect to climatic and other environmental conditions and in other respects all of which would make the question of matching the population sub groups with respect to variables other than diet a task of major proportions Furthermore the very task itself of performing a reasonable dietary survey is no small matter leaving aside the matching upon other variables Up to the present time this type of study has not been accomplished It is to be hoped that in time such a direct study will be done One corollary of this type of study would be to alter the diet of a very large sub segment of the population in a direction considered more favorable with respect to the outlook for coronary heart disease and then to compare the subjects who have altered their diet with a sub group matched otherwise but on an unaltered diet with respect to the incidence rate of clinical coronary heart disease In many ways such a study might be even more difficult than that of

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each such study is formidable The experiments involved are laborious expensive time-consuming and difficult to execute Indeed it is questionable that it is really possible to know the diet of a large series of patients under any circumstances other than institutionalization Thus the type of rigorous proof desired may be outside the realm of practical reality What then should be the position of the physician viewing the evidence concerning a favorable effect of a particular dietary alteration upon lipoprotein or Atherogenic Index values? Should he advise persons concerned with the prevention of clinical coronary heart disease (before or after an initial clinical manifestation) to make such a dietary alteration? There are three major possibilities which are of concern in appraising the prospect that a favorable dietary effect upon lipoprotein levels means a favorable effect upon coronary disease mortality First it is possible that lipoprotein level elevation and Atherogenic Index elevation may be direct causative factors in coronary heart disease as much of the evidence suggests strongly that they are If this be the true nature of the known association of coronary heart disease risk with Atherogenic Index value then there would be every reason to expect that lowering of the Atherogenic Index value would lower the rate at which new sub-clinical coronary heart disease develops and hence lower the future risk of *clinical* coronary heart disease

It is problematical at this time to know the extent to which such alteration in diet might be anticipated to reverse already existing coronary disease Whether such disease can be reversed will need to be determined with direct experimental evidence However if the nature of the association is that which has just been considered there is every reason to anticipate that lowering the levels of the lipoproteins will decrease the rate of development of *new* sub-clinical coronary heart disease A second possibility is that some third factor metabolic or otherwise accounts for the elevation in lipoprotein Atherogenic Index values and separately accounts for the development of coronary heart disease It is conceivable that dietary alteration can affect the lipoprotein levels favorably but fail to affect this hypothetical third factor In such an event the third factor still being operative might allow for the continued high rate of development of sub

determining the effect of diet in matched population sub groups without the question of *alteration* of diet

While the results from such studies would be highly desir able the many difficulties inherent in the direct approach to measurement of mortality from coronary heart disease in relation to diet or to alteration of diet are quite discouraging As a result, experimental work upon the relationship of diet to coronary heart disease has taken quite another path one that is highly favorable since not only does it provide information concerning the effect of diet upon known factors predisposing to coronary heart disease but also it allows development of some insight into mechanisms by which these factors operate Thus since the levels of lipoproteins from $S_f 0$ to $S_f 400$ are known to be directly related to the risk of future clinical coronary heart disease, it is entirely logical to determine the effect of any dietary factor or dietary alteration upon the level of all these lipoprotein classes If increased intake of a particular dietary factor is found to be asso ciated with elevation in level of any of these lipoprotein classes then a decreased intake of this dietary element can in general be anticipated to reduce the level of the particular lipoprotein class and thereby to produce a favorable effect with respect to reduction of coronary heart disease risk The reader will of course state that this represents a subtle transition from a dem onstration of a favorable effect upon lipoprotein level to a favor able effect upon the risk of clinical coronary heart disease

There can be no denial that the final and critical test of efficacy of any preventive or therapeutic measure is a direct test for reduction of *mortality* from coronary heart disease This *would require the study of a large series of cases subdivided* by careful randomization into two sub groups In one such sub group a particular dietary alteration would need to be intro duced whereas no such alteration would be made for the other sub group Comparison of coronary disease mortality rates at various follow up intervals thereafter would then be made This type of direct experiment constitutes the only final and rigorous proof There is every reason to contemplate such studies of various dietary alterations to obtain the direct and final proof of efficacy It must also be clear to the physician reader that

the S_f20 400 and generally also the S_f12 20 lipoproteins This latter group of patients is on the average characterized by a depression in the S_f0 12 lipoproteins Before considering the specific dietary management of these two lipoprotein disorders the general results of therapy must be emphasized In every patient with these disorders where the lipoproteins have been lowered appreciably and maintained lowered (now 15 patients) two signal results have been achieved First new xanthomata have failed to develop although the patient had been developing new lesions up to the time the treatment was instituted Second old lesions not only did not increase in size but began to decrease in size Many of the old lesions disappeared entirely in a period of several months to two years Lowering of lipoprotein levels in such patients was achieved in the main by dietary means Thus two different types of lipoprotein disorder each characterized by a development of a lesion extremely similar to the atheroma show regression of old lesions and inhibition of formation of new lesions when the lipoprotein levels are lowered From the similarity of the atheroma to the lesions of xanthomatosis it would be a most reasonable and very likely expectation that atheromas would behave similarly when lipoprotein levels are lowered although perhaps at a different rate To be sure the entire thesis of this book is being developed without the need to consider atheroma formation since the relationships developed all hold at the clinical level without any dependence upon pathology Nevertheless since it is probable that the mechanism by which lipoprotein levels and blood pressure come to be associated with clinical coronary heart disease is via their effect on atheroma formation cognizance of the information concerning patients with xanthomatosis helps strengthen the view that lowering of elevated lipoprotein levels and elevated blood pressures offers great promise for retardation of development of coronary heart disease Other important indirect evidence has been presented in detail concerning the lowered coronary heart disease mortality in insured overweight persons who subsequently reduced in weight (see Chapter IX) In that same discussion it was demonstrated that the average lipoprotein and blood pressure elevations in overweight persons accounts for essentially all the excessive coro

clinical coronary heart disease even though the dietary alteration had favorably affected the lipoprotein levels No evidence whatever exists for any such third factor It is simply being mentioned here as a hypothetical possibility, purely in the realm of speculation since it would be unscientific to deny its possible existence

It is strange that therapeutic nihilism in some quarters is so intense that the *possibility* of such a third factor is seized upon as a basis for denying any possible value of dietary reduction of blood lipoprotein levels in altering the rate of development of coronary heart disease The position of such nihilists is completely unscientific and essentially hopeless to cope with on any rational basis A third possibility must be evaluated with respect to the alteration of lipoprotein levels by dietary means It is conceivable that dietary alteration may affect some hypothetical *unproven other factor unfavorably with a net result of either no* retardation of coronary heart disease development or even an acceleration of the process Such a possibility cannot be denied on scientific grounds but the hypothetical noxious effect of diet on some hypothetical factor is at present a wholly undocumented speculative possibility No facet of the overall picture of this disease suggests the existence of such a factor Nihilism should not be allowed to retard clinical progress because of the remote possibility of existence of this factor Were this type of nihilism allowed to operate broadly in medicine the entire field of pharmaceutical therapeutics would long ago have ceased to exist

Much indirect evidence argues strongly that reduction in intensity of the predisposing factors will reduce the rate of progression of coronary heart disease One source of such evidence is the study of patients with xanthoma tendinosum or xanthoma tuberosum Such patients exist in the population at large because of the fact that on a familial basis they have an enormous derangement of one or another classes of lipoproteins the same lipoproteins which in the population at large are involved in the problem of coronary heart disease The xanthoma tendinosum patients are characterized by massive elevations of the S_f 0-12 lipoproteins and usually also the S_f 12-20 lipoproteins whereas the xanthoma tuberosum patients are characterized by elevation of

(1) The dietary fat intake both with respect to quantity and type of fat consumed

(2) The dietary carbohydrate intake

(3) The dietary calorie intake

Unfortunately a great deal of the investigative work that has been done at the clinical level with dietary alteration has suffered from certain major failings In some studies multiple dietary variables were being studied at once rendering interpretation of the results difficult or impossible For example patients advised concerning a restriction of the dietary fat intake have in many studies also been advised to restrict the total caloric intake with the result that weight loss was occurring during the dietary experiment Under such circumstances it is extremely difficult to draw any conclusions concerning the place of dietary fat restriction per se in management since there existed the uncontrolled variable of marked weight loss The inverse type of erroneous experiment has also been done Thus in many studies where total caloric intake was restricted there was a concomitant and essentially inadvertent restriction of fats carbohydrates and protein Effects upon lipoprotein levels observed during such caloric restriction may very well be the result of restriction of one or more of the specific components of the diet such as fat protein or carbohydrate The practical implications of erroneous interpretation of such experiments can be enormous If an effect truly attributable to fat restriction for example is credited to calorie restriction per se its applicability would be considered limited to those situations where calories could be restricted In truth such applicability should have extended to numerous situations where calorie restriction is not feasible but where fat restriction is feasible In many other dietary studies reported in the literature a variety of pharmacologically potent agents were prescribed at the same time the dietary modifications were made Dietary data derived from such studies must necessarily be viewed with suspicion until and unless the possibility can be ruled out that the pharmaceutical agents being concurrently administered had no effect upon the biochemical variable under consideration

Valid evidence concerning specific compositional factors in the diet is best derived from studies in which caloric intake is

nary heart disease in such persons Furthermore conclusive evidence is available that correction of overweight has in general the effect of reducing elevated lipoprotein levels and elevated blood pressures Thus it appears inescapable that the most probable basis for the beneficial effect of weight reduction is the lowering of lipoprotein levels and blood pressure Certain general principles govern any approach to reduction of coronary heart disease risk by manipulation of lipoprotein levels and blood pressure These principles apply not only to dietary methods but to any proposed pharmacologic approach or to their combination The real objective of a dietary program would be to affect the combination of lipoprotein and blood pressure factors such that the *net risk* of clinical coronary heart disease will be lowered Such net risk is the product of that due to the Atherogenic Index multiplied by that due to the blood pressure Leaving the pressure consideration aside for the moment coronary disease risk varies with Atherogenic Index Therefore, should a particular dietary regimen lower the S_f *0-12* and S_f *12-20* lipoprotein levels but *raise* the S_f *20-100* and S_f *100-400* lipoprotein levels the crucial issue would be whether or not the elevation in *Atherogenic Index resulting from the rise in* S_f *20-400 lipoproteins* was more than offset by the lowering in Atherogenic Index resulting from the fall in the S_f *0-12* and S_f *12-20* lipoproteins This is simply a situation where one must consider whether the regimen does more good than harm If the focus is solely upon which lipoprotein classes fall in level without consideration of possible rise in other classes serious errors in medical management can and do result This is by no means simply a hypothetical possibility Once it is assured that the dietary regimen has a *net* effect of lowering the Atherogenic Index it is still necessary to insure that it does *not* raise blood pressure significantly for if it does the net effect upon coronary heart disease risk might still be unfavorable

EFFECTS OF DIETARY FACTORS UPON SERUM LIPOPROTEIN LEVELS

Interest in dietary effects upon serum lipoproteins centers largely upon three factors

content fall in level e g S_f0 12 this may cause the total serum cholesterol level *to fall* even though a marked rise has occurred in lipoproteins poor in cholesterol content e g S_f20-400 The opposite trend of S_f20-400 lipoproteins from that of S_f0 12 lipoproteins may be of sufficient magnitude to cause a marked rise in Atherogenic Index and hence coronary heart disease risk even though the blood cholesterol level has fallen Therefore the *most* satisfactory data come from those studies which provide information concerning the fate of each lipoprotein class of interest with respect to coronary heart disease under the influence of any particular dietary manipulation

With respect to dietary fat intake two separate questions of major interest exist today with a large body of evidence now having built up concerning each The first concerns the *quantity* of dietary fat consumed and the effect of this upon the several blood lipoproteins of importance for coronary heart disease The second concerns the type of fat ingested rather than the quantity and the effect of type of fat upon the lipoprotein levels Two features of dietary fats have been of especial interest first whether the fat is of animal or vegetable origin and second the degree of saturation of the fat Since amount of fat and type of fat are the issues being considered evidence must be reviewed for studies where all dietary alterations were made at isocaloric levels so that weight loss is not involved Where type of fat per se is the issue not only is it necessary that total calories remain constant but also that the total *quantity* of fat consumed daily remains constant Further in such studies one is especially concerned about relatively long term effects of diet Therefore dietary studies involving relatively few days on any particular regimen are hardly meaningful with respect to the longer term effects of interest namely whether or not dietary alterations can be made which will produce and maintain lipoprotein alterations of a desirable character over a long period of time Long term studies were performed during 1950 and 1951 which contrast diets high in fat intake with those low in total fat intake Nichols and co workers[18] have reported these carefully controlled studies Diets high in fat of animal origin and those high in fat of vegetable origin have both been contrasted with low fat diets

maintained constant This is especially important since for obscure reasons many physicians and lay people alike equate dietary restriction with calorie restriction and are inclined to attribute nearly any effect obtained by dietary means to calorie restriction and weight loss If dietary manipulation of coronary heart disease risk rested wholly upon calorie restriction and weight loss, a great deal could be done clinically but of greater importance would be the need for management for the large fraction of the population in whom weight loss and calorie restriction is not feasible but in whom a high coronary heart disease risk still exists Therefore careful delineation of which dietary effects depend upon specific food factors and which upon calorie restriction per se is of intense practical importance

THE DIETARY FAT INTAKE

Dietary fat has been of interest with respect to coronary heart disease for a very long time in part because of some of the apparent geographic associations between dietary fat intake blood lipid levels and coronary heart disease early alluded to by Snapper[26] concerning such associations in China However many of the earlier studies of the relationship of diet with coronary heart disease via the association of both with blood lipid levels are now primarily of historical interest either (a) because the blood lipid methods utilized were very crude or (b) because the blood lipid measurements then available such as for example a serum cholesterol measurement failed to provide adequate information concerning the fate of each of the important lipoprotein classes with respect to dietary manipulation A blood lipid measurement which does not adequately reflect what is happening to all the lipoprotein classes between S_f0 and S_f400 can give rise to seriously erroneous impressions concerning the potential efficacy of the dietary alteration Examples are now well known where a particular dietary manipulation can elevate the level of one band of lipoproteins while depressing the level of other bands An approximate measure of the lipoprotein levels such as the serum cholesterol level reflects only part of the entire change If certain lipoproteins rich in cholesterol

TABLE XXXVII

Long Term Effects of Diets High in Fat of Animal Origin Versus Diets Low in Total Fat Upon Serum Lipoprotein Levels and Atherogenic Index Values

(Both diets identical in calorie intake[a])

Subject	During Diet High in Fat of Animal Origin	During Diet Low in Total Fat	Change
Mean S_f 0-12 Lipoprotein Levels (mg/100ml)			
1	394	335	− 59
2	463	333	− 130
3	466	295	− 171
4	341	260	− 81
5	365	273	− 82
Mean for 5 Subjects	405.8	299.2	− 104.6
Mean S_f 12-20 Lipoprotein Levels (mg/100ml)			
1	54	56	+ 2
2	100	62	− 38
3	105	63	− 42
4	32	30	− 2
5	65	44	− 21
Mean for 5 Subjects	71.2	51.0	− 20.2
Mean S_f 20-100 Lipoprotein Levels (mg/100ml)			
1	126	169	+ 43
	141	150	+ 9
3	129	132	+ 3
4	40	56	+ 16
5	137	142	+ 5
Mean for 5 Subjects	114.6	1[illegible]9.8	+ 15.2
Mean S_f 100-400 Lipoprotein Levels (mg/100ml)			
1	125	308	+ 183
2	100	160	+ 60
3	72	102	+ 30
4	17	33	+ 16
5	56	3	+ 17
Mean for Subjects	[illegible]4.0	135.2	+ 61.2
Mean Atherogenic Index Values (in units)			
1	93	127	+ 34
2	105	93	− 8
3	100	81	− 19
4	50	47	− 3
	9	73	− 9
Mean for Subjects	9[illegible].1	85.2	− 0.9

[a] The low fat dietary period is a high-carbohydrate period since carbohydrate calories replaced those lost from fat

in those studies The study periods utilized by Nichols for each type of diet were sufficiently long that transitional effects resulting from dietary alteration were minimized Five male subjects participated in that long term dietary study, taking all meals at a hospital diet table save for breakfast which was standard and was eaten at home Samples of blood on all five subjects were drawn once weekly divided into two aliquots and analyzed in duplicate *to minimize experimental errors Furthermore*, all dietary periods were of eleven or twelve weeks in duration Therefore the mean levels of lipoproteins for each particular *dietary composition reflect no fewer than 22 blood analyses for* each of the subjects studied Since the overall dietary periods under consideration include the first week after the person was *on the new* diet during which any transitional effects may have existed the average effects measured for the entire period on a particular diet must actually have been even larger than reported if the transitional periods are characterized by intermediary lipoprotein values Therefore all the changes proved to be significant were evaluated on a conservative basis The diets that were consumed by the individuals during these various periods do not represent formula diets Instead they were diets prepared in a diet kitchen with kitchen tested recipes and arranged in menus planned in such a manner that a person could enjoy meals over a long period of time with one or another of these diets What such diets may lack in ultimate chemical precision they undoubtedly gain in provision of information concerning practical aspects of dieting over long periods under usual physiologic circumstances of living The data comparing the long term lipoprotein levels on a diet high in fat primarily of animal origin and a diet low in fat are presented in Table XXVII Maintenance of iso-caloricity was achieved by carbohydrate supplementation in the low fat period The regularity of fall in the level of S_f0 12 lipoproteins which occurs with substitution of a diet containing 103 grams of fat per day (93% of which is of animal origin) by a diet containing 18 grams of fat is notable The S_f12 20 lipoproteins behave in general similarly to the S_f0 12 lipoproteins falling in level when the high animal fat intake is replaced by a diet low in total fat intake The behavior of

TABLE XXXVIII

LONG TERM EFFECTS OF DIETS HIGH IN FAT OF ANIMAL ORIGIN VERSUS DIETS HIGH IN VEGETABLE OIL UPON SERUM LIPOPROTEIN LEVELS AND ATHEROGENIC INDEX VALUES

(Both diets containing same total quantity of fat and calories)

Subject	During Diet High in Fat of Animal Origin	During Diet High in Vegetable Oil	Change
Mean S_f 0-12 Lipoprotein Levels (mg/100ml)			
1	394	290	− 104
2	463	316	− 147
3	466	284	− 182
4	341	269	− 72
5	365	299	− 66
Mean for 5 Subjects	405.8	291.6	− 114.2
Mean S_f 12-20 Lipoprotein Levels (mg/100ml)			
1	54	47	− 7
2	100	70	− 30
3	105	62	− 43
4	32	23	− 9
[illegible]	65	53	− 12
Mean for 5 Subjects	71.2	51.0	− 20.2
Mean S_f 20-100 Lipoprotein Levels (mg/100ml)			
1	[illegible]	142	+ 16
2	141	127	− 14
3	129	97	− 32
4	40	30	− 10
5	137	[illegible]	+ 10
Mean for 5 Subjects	114.6	108.6	− 6.0
Mean S_f 100-400 Lipoprotein Levels (mg/100ml)			
1	125	[illegible]	+ 10
2	100	109	+ 9
3	72	[illegible]	− 12
4	17	18	+ 1
[illegible]	56	61	+ 5
Mean for 5 Subjects	74.0	76.6	+ 2.6
Mean Atherogenic Index Value			
1	93	86	− 7
[illegible]	106	[illegible]	− 21
3	100	67	− 33
4	50	39	− 11
5	89	[illegible]	− 6
Mean for 5 Subjects	86.1	[illegible]	− 15.5

S_f20-100 and S_f100-400 lipoproteins accompanying this dietary shift was somewhat surprising. Both S_f20-100 and S_f100-400 lipoproteins rose appreciably, though variably among the subjects when the diet high in animal fat was replaced by that low in fat but with the lost fat calories replaced by carbohydrate. The effect is sufficiently large to be well beyond any question of simply a sampling error and it has been confirmed repeatedly both here and elsewhere in the world.[28, 29] There is no question that the low-fat, high-carbohydrate dietary period is associated with a rise in level of the S_f20-100 and S_f100-400 lipoprotein classes. Two possible explanations of the observed rise is S_f20-100 and S_f100-400 lipoproteins with this dietary shift are (1) that a fat deficiency might be responsible or (2) the possibility (which is now known to be correct) that the increase in carbohydrate intake necessary to maintain isocaloricity of the diet is itself responsible for the striking rise in S_f20-100 and S_f100-100 lipoproteins. The conclusion that it is the carbohydrate supplement rather than a possible fat deficiency which is responsible for the rise in S_f20-100 and 100-400 lipoproteins is based upon many sources of evidence to be developed below. First, however, it is important to compare two other dietary periods in this same study of Nichols and co-workers. These two periods, again isocaloric so that weight loss did not occur, both provided the same total quantity of dietary fat but the source and type of fat differed markedly in these two periods. Thus approximately 100 grams of fat were present in the daily diet of both periods. In one case the fat was primarily from animal sources, whereas the fat was primarily from vegetable sources in the other dietary period. In the period of high vegetable fat ingestion it was the liquid, relatively unsaturated cottonseed oil which was utilized. The lipoprotein comparisons for these two dietary periods are presented in Table XXVIII. It is to be noted from these data that the shift from 100 grams of fat primarily from animal sources to 100 grams of fat primarily in the form of vegetable oil, but with the total caloric intake and fat content of the diet maintained constant, that the S_f0-12 and S_f12-20 lipoprotein levels fell and did so to essentially the same extent as they did when the diet providing 100 grams of fat of animal origin was replaced by a low-fat diet

urated fatty acids in vegetable oil? Second is the elevation in S_f0 100 and 100-400 lipoproteins observed on the high carbohydrate intake in contrast with the levels observed on both the diet high in animal fat and on that high in vegetable oil due to the increased carbohydrate intake per se or to some type of deficiency in the low fat high carbohydrate diet?

With respect to the first question there exists a very important corollary namely whether the addition of vegetable oil to a diet *unaltered in animal fat content* can be expected to overcome the noxious lipoprotein elevating effect of a diet high in fat of animal origin If vegetable oil provides some hypothetical positively beneficial substance then it would be anticipated that S_f0 12 and S_f12 20 lipoprotein levels would *rise* when the vegetable oil diet is replaced by a low fat diet since the hypothetical protective substance would be absent The direct studies (see Tables XXVII and XXVIII) show that *no such rise* was observed *upon shifting* from the diet high in vegetable oil to that low in total fat intake This militates strongly *against* the concept that any beneficial protective substance exists in vegetable oil which helps to reduce S_f0 12 and S_f12 20 lipoprotein levels On the other hand if the animal fat contains a possible noxious substance the S_f0 12 and S_f12 20 lipoprotein levels would be expected to fall comparably *either* with a replacement of the animal fat by vegetable oil or by a shift from a diet high in animal fat to a diet low in total fat intake *This is precisely what is observed in carefully controlled studies* It is reasonable to conclude therefore that fat of animal origin contains some factor (or factors) endowed with the noxious capability of elevating S_f0 12 and S_f12 20 lipoprotein levels Several other investigators throughout the world have in recent years studied the differences between diets high in fat of animal origin and those high in oil of vegetable origin utilizing the serum cholesterol level as a criterion of effects of various diets upon the blood lipoproteins As a result of statements in the reports of some of these investigations there is current a notion in some quarters that certain vegetable oils contain a beneficial substance capable of lowering serum cholesterol levels While the serum cholesterol level is not an adequate guide for blood lipoprotein response the

Further the S_f20 100 and S_f100 400 lipoprotein levels did not rise when vegetable oil was used to replace the animal fat instead of the use of carbohydrate for such replacement Therefore a diet which maintains the fat intake constant but which replaces animal fat with vegetable oil is completely like the low fat diet in *one respect,* namely that both diets are characterized by the same degree of lowering of the S_f0 12 and S_f12 20 lipoproteins when contrasted with a diet high in animal fat The diet high in vegetable oil and the low fat diet (high in carbohydrate) however *differ* in another very important respect namely whereas the S_f20 100 and S_f100-400 lipoprotein levels rise when carbohydrate is used as the replacement for the animal fat they do not rise when vegetable oil is the replacement In summary the S_f0 12 and S_f12 20 lipoproteins are at the same level on a diet high in vegetable oil or a diet high in carbohydrate in both of which cases the levels are much lower than on the diet high in animal fat The S_f20 100 and S_f100-400 lipoproteins are at essentially the same level on a diet high in animal fat or vegetable oil in both cases much lower than on a diet high in carbohydrate All four classes of lipoproteins are of great importance because of their predictive association with clinical coronary heart disease Hence a dietary factor that affects the blood level of any one of them must be carefully weighed in any program designed to alter the risk of coronary heart disease The remarkable dissociation between the effect of dietary factors on the S_f0 12 and 12 20 lipoproteins from the effect on the S_f20 100 and 100-400 lipoproteins points up the critical necessity of knowledge for a particular dietary factor of what it does to all of these lipoprotein classes Reliance upon any crude measure which fails to discern opposite trends in level for one class of lipoproteins from those for other classes is of real clinical danger

Two fundamental questions of immediate clinical importance present themselves as a result of these findings with respect to diet First is the marked elevation in S_f0 12 and S_f12 20 lipoprotein levels on a diet high in animal fat relative either to one high in vegetable oil or to a low fat diet the result of action of some noxious factor in or attribute of animal fat or is it a manifestation of a deficiency of some factor such as the unsat

a rise in the serum level of s_f20 100 and s_f100-400 lipoproteins on a high carbohydrate diet would elevate the blood cholesterol level provided no fall in the level of other cholesterol-containing lipoproteins obscured this rise When Ahrens shifted his patient isocalorically from a diet where 70% of the calories were from corn oil to one where only 10% of the calories came from corn oil he was in effect shifting the patient from a very low car bohydrate diet to a very high carbohydrate diet This increase in carbohydrate intake is itself quite adequate to account for the rise in blood cholesterol levels (via raising s_f20 100 and s_f100 400 lipoprotein levels) he observed without invoking the con clusion he drew that corn oil in large amounts is beneficial His positive effect of corn oil is almost certainly the effect of lower ing the carbohydrate intake of the patient

Beveridge and co workers[63] did short term experiments of a somewhat similar nature to those of Ahrens They showed that the blood cholesterol level fell when a low fat diet was com pared with a usual mixed diet Then when a large fraction of the carbohydrate of the low fat diet was replaced by corn oil they observed a further lowering of the serum cholesterol level This lowering was attributed by Beveridge and co-workers to the beneficial effect of corn oil No consideration was given by them to the possibility that the lowering of blood cholesterol levels might have been the result of the simultaneous removal of a large amount of the carbohydrate from the diet Since the removal of a great quantity of dietary carbohydrate in the Bev eridge experiment would be expected to lower the s_f20 100 and s_f100-400 lipoprotein levels and hence lower the blood choles terol level because of the cholesterol content of these lipopro teins there is no indication whatever for them to have attributed the observed changes to any presumed beneficial effect of corn oil Numerous other studies abound in the medical literature purporting to show a positively beneficial effect of some sub stance in vegetable oils but essentially all of them suffer from the oversights described for the specific studies considered here

At present there exists no valid evidence for the existence of a beneficial factor in vegetable oils or for an essential position of the vegetable oils in the human dietary with respect to the phe

erroneous notions do not arise from this source, but rather from faulty interpretation of the experimental findings. Thus Kinsell[60] replaced animal fats with such vegetable oils as corn oil and observed a lowering of the serum cholesterol level. He drew the conclusion that there must be something positively beneficial about corn oil. Since corn oil contains an appreciable quantity of the unsaturated fatty acid linoleic acid, he has advanced the idea that such unsaturated fatty acids as linoleic acid are "essential fatty acids for the human with respect to the control of serum cholesterol levels." Kinsell apparently did not even consider seriously the alternative explanation of a noxious substance in fat of animal origin. Further, his studies were not controlled by the inclusion of a comparison of the high vegetable oil intake with a low fat intake. Therefore there is no valid reason to consider from his work that linoleic acid is "essential" with respect to the maintenance of low serum cholesterol levels, nor to consider that vegetable oils contain any positively beneficial agent capable of effecting a lowering of blood lipoprotein levels.

Ahrens and his co-workers[61] *studied patients on formula* diets with variation in the type of fat ingested and in the fraction of the total caloric intake provided by fat. He reported for one patient that when the proportion of total calories in the diet was varied upward from 40% to 70% and downward from 40% to 10%, while maintaining protein and total calorie intake constant, there was a rise in blood cholesterol level on the diet with 10% of the calories contributed by corn oil and a prompt decline in blood cholesterol level on the diet in which 70% of the calories were contributed by corn oil. He concluded, "the reduction in lipid levels may be more pronounced with a high intake of certain specific fats." There is clearly implied in this statement that a fat such as corn oil provides some specific beneficial agent. There is no reason to accept this conclusion from data such as those of Ahrens and co-workers. In the studies of Nichols and co-workers[46] (See Table XXXVII) it was found that a high carbohydrate intake is generally associated with a rise in the serum level of S_f20-100 and S_f100-400 lipoproteins. These particular lipoproteins have cholesterol in them to the extent of approximately 13% by weight[6]. Therefore it would be anticipated that

for a decision as to whether dietary cholesterol itself might be the noxious agent involved in diets high in animal fat Ahrens[85] has presented important evidence that *saturated* vegetable fats behave more like animal fats with respect to effect upon blood lipids when they do like the most unsaturated vegetable oils such as corn oil He suggested that perhaps the saturated fats may themselves be the noxious substances It is certainly true that animal fats (*excluding* marine animal fats) are on the average more highly saturated than are such vegetable fats as unhydrogenated corn oil cottonseed oil and safflower oil Bronte Stewart and co workers[86] found that *hydrogenated* groundnut oil produced higher blood cholesterol levels in human subjects than did dietary intake of equivalent amounts of unhydrogenated ground nut oil However they also found that the effect of hydrogenated ground nut oil in raising blood cholesterol levels was slight compared with that produced by the dietary intake of the same *quantity* of fat in the form of egg yolks

It appears at present that the natural fats of animal origin such as dairy fat meat fat and egg fat have the greatest effect in elevation of S_f0 12 and S_f12 20 lipoprotein levels Saturated vegetable fats either those occurring naturally such as coconut oil or those produced by hydrogenation of unsaturated oils have an adverse effect upon S_f0 12 and S_f12 20 lipoproteins but probably not to the same extent as the animal fats The unsaturated vegetable oils while *not beneficial* with respect to lowering of S_f0 12 and S_f12 20 lipoprotein levels are at least neutral in this regard This latter fact is of itself of tremendous practical consequence since it allows for the incorporation of vegetable oils into a diet (with attendant increase in palatability and satiety value) that is still adequately restricted in saturated vegetable fas and animal fats to achieve the desirable lowering of elevated S_f0 12 and S_f12 20 lipoprotein levels

DIETARY CARBOHYDRATE INTAKE

The second major problem involved in the effects of diet upon serum lipoprotein levels centers around the elevation of S_f20 100 and S_f100-400 lipoprotein levels during the low fat

nomenon of control of blood lipid or lipoprotein levels It is clear from all studies that vegetable oils differ from animal fats, with all the evidence pointing to a noxious effect of the fats of animal origin rather than to a beneficial agent in the vegetable oil The corollary question of whether or not the noxious effect of animal fat can possibly be overcome by *supplementation* of the diet by vegetable oil *without* removal of part or all of the animal fat from the diet comes up repeatedly The experiments discussed up to this point do not of themselves allow for an answer to this highly pertinent question since they involved the *replacement* of animal fat by vegetable oil Some poorly controlled studies have been reported in the literature where ostensibly a *supplement* of vegetable oil was provided in the daily diet and where a fall in blood lipid levels was observed However review of the protocols of such studies showed that these were actually *replacement* experiments where either dietary animal fat or carbohydrate or both were *lowered* concurrently with the supposed supplementation of the diet by vegetable oil Since no light is shed upon the problem at hand by such studies they do not merit specific comment here One carefully performed supplementation study has recently reported by Perkins and Wright[64] These workers provided a supplement of 50 grams of safflower oil in the diet of 24 subjects for a period of 6 to 7 weeks Safflower oil is very rich in linoleic acid the fatty acid claimed by Kinsell to be essential for lowering of the blood cholesterol level *No lowering of cholesterol levels could be demonstrated to occur as a result of safflower oil supplementation* in the careful study of Perkins and Wright It therefore appears necessary to conclude that the noxious effect of animal fat cannot be overcome by provision of a vegetable oil supplement even when that vegetable oil is one of the richest in its content of linoleic acid

It is a matter of practical as well as academic interest to identify the nature of the noxious agent (or agents) present in fat of animal origin which can effect an elevation of *S_f0 12 and S_f12 20 lipoprotein levels In most of the reported studies with* dietary animal fat the diet also provided a reasonably high content of cholesterol *per se* None of the studies discussed allow

for a decision as to whether dietary cholesterol itself might be the noxious agent involved in diets high in animal fat. Ahrens[6] has presented important evidence that *saturated* vegetable fats behave more like animal fats with respect to effect upon blood lipids than they do like the most unsaturated vegetable oils such as corn oil. He suggested that perhaps the saturated fats may themselves be the noxious substances. It is certainly true that animal fats (excluding marine animal fats) are on the average more highly saturated than are such vegetable fats as unhydrogenated corn oil, cottonseed oil, and safflower oil. Bronte-Stewart and co-workers[68] found that *hydrogenated* groundnut oil produced higher blood cholesterol levels in human subjects than did dietary intake of equivalent amounts of unhydrogenated ground nut oil. However, they also found that the effect of hydrogenated ground nut oil in raising blood cholesterol levels was slight compared with that produced by the dietary intake of the same *quantity* of fat in the form of egg yolks.

It appears at present that the natural fats of animal origin such as dairy fat, meat fat, and egg fat have the greatest effect in elevation of S_f 0-12 and S_f 12-20 lipoprotein levels. Saturated vegetable fats, either those occurring naturally such as coconut oil or those produced by hydrogenation of unsaturated oils, have an adverse effect upon S_f 0-12 and S_f 12-20 lipoproteins but probably not to the same extent as the animal fats. The unsaturated vegetable oils, while *not beneficial* with respect to lowering of S_f 0-12 and S_f 12-20 lipoprotein levels, are at least neutral in this regard. This latter fact is of itself of tremendous practical consequence since it allows for the incorporation of vegetable oils into a diet (with attendant increase in palatability and satiety value) that is still adequately restricted in saturated vegetable fas and animal fats to achieve the desirable lowering of elevated S_f 0-12 and S_f 12-20 lipoprotein levels.

DIETARY CARBOHYDRATE INTAKE

The second major problem involved in the effects of diet upon serum lipoprotein levels centers around the elevation of S_f 20-100 and S_f 100-400 lipoprotein levels during the low fat

high carbohydrate dietary periods Is this elevation the result of the high carbohydrate intake or the result of some type of deficiency encountered because of the low fat intake? Data were already present for weight reduction studies (see Chapter IX) which help provide the answer to this question In those studies a 1000 calorie low fat low carbohydrate diet was utilized If fat deficiency were responsible for an elevation in S_f20 100 and S_f100-400 lipoproteins it would have been anticipated that the S_f20 100 and S_f100-400 would have become elevated in level during the weight reduction program *but this did not occur* Instead the S_f20 100 and S_f100 400 lipoprotein levels *fell* during the weight reduction period Since the 1000 calorie diet is a low carbohydrate diet this is precisely the result that would have been anticipated if these lipoprotein classes are sensitive to the dietary carbohydrate intake rising with increased carbohydrate intake and falling with decreased carbohydrate intake The clinical experience of the author in numerous patients has consistently confirmed this conclusion namely that S_f20 100 and S_f100 400 lipoprotein levels are largely controlled by the dietary carbohydrate intake Indeed the most effective dietary procedure for reducing elevated S_f20 100 and S_f100 400 lipoprotein levels is the reduction in the patient s habitual dietary carbohydrate intake

The mechanism by which carbohydrate excess in the diet produces elevation of S_f20 100 and S_f100 400 lipoprotein levels remains unexplained at this time Two possible explanations currently under consideration are that (a) dietary carbohydrate in abundance spares the utilization of fat from S_f20 100 and S_f100 400 lipoproteins from the blood for energy purposes and hence results in an increase in their levels or (b) that the conversion of dietary carbohydrate to fat either for storage or utilization involves a transport phase during which the S_f20 100 and S_f100 400 lipoprotein levels are elevated Whatever be the precise biochemical mechanism the practical implications of the carbohydrate effect for the prevention and treatment of clinical coronary heart disease are extensive

Thus far consideration has been given to the dietary intake of fat both with respect to quantity and origin and the dietary intake of carbohydrate All of the studies which show the effects of alteration of these dietary factors have been done at isocaloric levels with the subjects neither gaining nor losing weight Hence calories were not involved as a variable It cannot be overemphasized that *without* alteration of weight or calorie intake blood lipoproteins *can* be altered by certain dietary shifts However the lipoprotein alterations which occur when calorie intake and weight are altered are of much interest The changes in blood lipoproteins both in experimental alteration of weight and in the natural experiment where individuals gain or lose weight over a long period of time are presented in Chapter IX in the general discussion of overweight correction of overweight and their relationship to lipoprotein levels Associated with a correction of overweight by calorie restriction there occurs a fall in blood level in all the major classes of lipoproteins S_f 0-12 12-20 20-100 and 100-400 In the light of the immediately previous discussion the probable explanation for the fall in lipoproteins which is observed when an individual who is overweight goes on a calorie restricted diet can be evaluated A person who is habitually eating more calories than he needs to maintain an ideal weight is taking in too many calories either in the form of protein of fat or of carbohydrate or of some combination of these Of these three it is most likely that any real excess in calories is coming in the form of an excess of fat and/or carbohydrate as a result of the types of habitual diets generally consumed by Americans Of the excess fat which would be consumed undoubtedly a fair share would be of the relatively saturated varieties either animal fat or hydrogenated vegetable fat This being the case such a person might be anticipated to show in general some elevation in the S_f 0-12 and 12-20 levels as a result of his habitual excessive fat intake or some elevation in the S_f 20-100 and 100-400 levels as a result of a habitual excess carbohydrate intake or both Therefore when such a person goes on a calorically restricted diet in the effort to correct over

high carbohydrate dietary periods Is this elevation the result of the high carbohydrate intake or the result of some type of deficiency encountered because of the low fat intake? Data were already present for weight reduction studies (see Chapter IX) which help provide the answer to this question In those studies a 1000 calorie low fat low carbohydrate diet was utilized If fat deficiency were responsible for an elevation in s_f20 100 and s_f100-400 lipoproteins it would have been anticipated that the s_f20 100 and s_f100 400 would have become elevated in level during the weight reduction program *but this did not occur Instead the s_f20 100 and s_f100-400 lipoprotein levels fell during* the weight reduction period Since the 1000 calorie diet is a low carbohydrate diet this is precisely the result that would have been anticipated if these lipoprotein classes are sensitive to the dietary carbohydrate intake rising with increased carbohydrate intake and falling with decreased carbohydrate intake The clinical experience of the author in numerous patients has consistently confirmed this conclusion namely that s_f20 100 and s_f100 400 lipoprotein levels are largely controlled by the dietary carbohydrate intake Indeed the most effective dietary procedure for reducing elevated s_f20 100 and s_f100 400 lipoprotein levels is the reduction in the patient s habitual dietary carbohydrate intake

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saturated vegetable fat can be replaced by any of a variety of vegetable oils such as cottonseed oil corn oil safflower oil sun flower oil soya oil or peanut oil without fear of producing a rise in lipoproteins through addition of these vegetable oils In other words the vegetable oils of these type are essentially with out any effect favorable or unfavorable However the absence of any adverse or beneficial effect is in itself a highly beneficial feature since this means that the diet that is possible for such an individual produces no real loss in palatability satiety value and enjoyment relative to that which utilizes the animal fats Such a diet is much more readily accepted and enjoyed by a patient than would be a low fat diet If the patient with elevated s_f0 12 or s_f0 20 lipoprotein levels is not overweight he can ill afford to lose any of his dietary calories by simple removal of the animal or saturated fat from his diet He needs replacement of calories to avoid weight loss But loss of weight has been shown above *not* to be an essential part of this problem of lowering the s_f0 12 or s_f0 20 lipoproteins It is rather a question of the type of dietary fat consumed Therefore even though such an indi vidual maintains his calories by replacement with one of the vegetable oils and thereby maintains his weight he will generally experience a favorable reduction in lipoprotein levels On the *other hand* if such a patient is overweight there would be every reason to attempt to reduce some of the calories in his diet and in this attempt to concentrate upon those calories deriving from saturated vegetable fat or animal fat since they are for him the offenders involved in maintaining high s_f0 12 and 12 20 levels

There exist many persons who are characterized by low levels of the s_f0 12 and 12 20 lipoproteins but who demonstrate very high levels of s_f20 100 or s_f100-400 lipoproteins or both The elevation in these classes of lipoproteins is sufficient in many such patients to produce *markedly elevated* Atherogenic Index values and hence high coronary heart disease risks in spite of their low levels of the s_f0 12 and 12 20 lipoproteins In this type of patient efforts to decrease the coronary heart disease risk through the advocacy of a low fat diet or of a replacement of animal fat with vegetable oil will be to no avail in the vast majority of cases for the lipoproteins that are elevated in these persons are *not*

weight and when he reduces some of the animal fat (or saturated fat intake) in his diet as well as some of the carbohydrate intake in his diet, it is not surprising that we should see an average trend downward of the four classes of lipoproteins. During calorie restriction dietary alterations are being made which are *known* to affect either one group of lipoproteins or another or both. Whether or not any factor beyond the reduced animal fat intake or the reduced carbohydrate intake or both is responsible for the fall in lipoproteins which occurs when an individual restricts dietary calories and loses weight cannot be stated. However, there exists no positive evidence that any such effect operates over and above that which can be explained by the animal fat restriction and/or the carbohydrate restriction in such a low calorie diet. The overweight individual who is taking in too much animal or saturated fat and too much carbohydrate habitually has of course the best opportunity to reduce lipoprotein levels since he can to good advantage lower two types of substances in the diet which are known to have unfavorable influences upon the blood lipoproteins, the Atherogenic Index and the coronary heart disease risk.

THE PRACTICAL CLINICAL APPLICATIONS OF THE DIETARY FINDINGS

It is evident that no single dietary regimen can be prescribed that will cover all the types of situations encountered with respect to blood lipoprotein distribution *in the effort to* reduce clinical coronary heart disease risk. Thus there are *individuals who carry an excessive risk of coronary heart disease* almost wholly because of a marked elevation of the S_f 0-12 and 12-20 lipoproteins *and who show either usual or lower than usual levels of the S_f 20-100 and 100-400 lipoproteins.* For this type of individual there is excellent reason to prescribe a trial of a diet restricted in fat of animal origin or saturated fat of vegetable sources. In many such individuals the lipoproteins of the S_f 0-20 class will fall markedly, there will be a corresponding improvement in the Atherogenic Index and the patient may be expected to benefit. The calories lost from the animal fat or

saturated vegetable fat can be replaced by any of a variety of vegetable oils such as cottonseed oil corn oil safflower oil sun flower oil soya oil or peanut oil without fear of producing a rise in lipoproteins through addition of these vegetable oils In other words the vegetable oils of these type are essentially with out any effect favorable or unfavorable However the absence of any adverse or beneficial effect is in itself a highly beneficial feature since this means that the diet that is possible for such an individual produces no real loss in palatability satiety value and enjoyment relative to that which utilizes the animal fats Such a diet is much more readily accepted and enjoyed by a patient than would be a low fat diet If the patient with elevated S_f0 12 or S_f0 20 lipoprotein levels is not overweight he can ill afford to lose any of his dietary calories by simple removal of the animal or saturated fat from his diet He needs replacement of calories to avoid weight loss But loss of weight has been shown above not to be an essential part of this problem of lowering the S_f0 12 or S_f0 20 lipoproteins It is rather a question of the type of dietary fat consumed Therefore even though such an individual maintains his calorie by replacement with one of the vegetable oils and thereby maintains his weight he will generally experience a favorable reduction in lipoprotein levels On the other hand if such a patient is overweight there would be every reason to attempt to reduce some of the calories in his diet and in this attempt to concentrate upon those calories deriving from saturated vegetable fat or animal fat since they are for him the offenders involved in maintaining high S_f0 12 and 12 20 levels

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sensitive to the composition or quantity of fat in the diet. Rather, *they are very sensitive to the quantity of carbohydrate in the diet.* Therefore, in clinical practice, such patients should be treated with a diet restricted in carbohydrate. Here again, vegetable oils represent a very useful agent in the diet, for the calories that are lost from carbohydrate can be supplanted by those from vegetable oils with excellent palatability of the diet. This is especially important in the patient who is already at ideal weight or is underweight and cannot afford to lose such calories. For the patient with high S_f 20-100 and 100-400 lipoprotein levels who is overweight and who can and should lose some of the calories, his caloric restriction and the correction of his overweight can be made more *meaningful* if such caloric restriction is focussed on the carbohydrate intake.

Lastly, physicians will encounter patients who have what may be called "across the board" elevations of all four important classes of lipoproteins. These patients require a still different dietary approach. If the patient is overweight, some of the calories which are in excess should be deleted from the diet both in the form of animal fat and of carbohydrate. In this situation the calories lost require no replacement. If such a patient is not *overweight*, then the appropriate diet still would require reduction of the intake of animal fat (or saturated vegetable fats) on the one hand *and* of carbohydrate on the other. This means that supplementation of the calories required to maintain weight would have to come from vegetable oils. If attention is paid only to one class of lipoproteins, full advantage of the dietary approach is hardly being taken for the particular patient, and in certain *instances serious errors of management can eventuate.* For example, if a patient has an elevation of S_f 20-100 and 100-400 lipoproteins (the carbohydrate-sensitive group) and if the physician, failing to realize the indication for a low-carbohydrate diet, prescribes a low-fat diet for this patient, he will fail to accomplish his objective because he is not changing any dietary factor that can be expected to influence those lipoproteins of importance in such a patient. *Secondly, he may do some* real harm because of the fact that many patients who restrict fat in their diets replace the fat freely with carbohydrate. In this particular

type of patient sensitive to carbohydrate the additional carbohydrate can be regarded as an insult which will raise S_f20 100 and S_f100-400 lipoprotein levels still further There are many patients however who can replace some of their animal fat with carbohydrate in the effort to lower their S_f0 20 lipoproteins by animal fat (or saturated fat) restriction because they are not very sensitive to the carbohydrate effect and will not experience any appreciable rise in S_f20 100 and 100-400 lipoproteins This can only be determined by direct trial in each particular patient However it is through the careful assessment both of the S_f0 20 and the S_f20-400 lipoproteins that one can with certainty rather than with guesswork determine whether a particular dietary regimen is influencing a patient in a favorable direction The lipoprotein measurements can aid the physician to appreciate whether further dietary changes are still indicated including the type of dietary changes indicated to try to achieve desired results

The irrational blanket use of a particular dietary regimen in all persons irrespective of lipoprotein distribution is not to be condoned Such generalizations as we all eat too much fat or we all eat too much animal fat merely reflect a lack of understanding of major progress in the understanding of dietary factors in relation to risk of coronary heart disease There is of course some element of truth in such generalizations but there is also a considerable element of falsehood in them For a large segment of the population the statement that we eat too much carbohydrate is much closer to reality Action based upon uncritical generalizations may do almost as much medical harm as good and in individual cases we can be certain that more harm than good will result It can be regarded as fortunate that enough knowledge is now available for a critical approach to dietary management and such knowledge should be fully utilized by the practicing physician

Chapter XI

CIGARETTE SMOKING AND CORONARY HEART DISEASE

It is commonplace in medical practise to find that physicians advise patients with clinically manifest coronary heart disease to cut down on smoking especially those individuals with a history of heavy cigarette smoking Evidently the impression has been widespread medically that in some way cigarette smoking is unfavorable for the patient with clinically documented coronary heart disease Some of this advice is based upon the suspicion that tobacco may produce coronary artery vasoconstriction which in the face of an already embarrassed coronary blood flow is regarded as highly unfavorable All this pertains to the person with already established clinical coronary heart disease Of even greater importance is the question of whether or not cigarette smoking is associated with any increased risk of *future* clinical coronary heart disease in the vast bulk of the population at large in overt health This question might be put another way Does cigarette smoking accelerate the rate of development of *subclinical* coronary heart disease? On this question general medical opinion has for long been divided largely of course because sound evidence upon which a meaningful answer could be based simply was unavailable Several significant avenues of approach may be contemplated in the effort to answer this question Information is now available from scientific observation not only to answer the question in the affirmative namely that cigarette smoking is associated with acceleration of the rate of development of subclinical coronary heart disease but also to understand the probable mechanisms through which the effect is mediated

RETROSPECTIVE EVIDENCE CONCERNING CIGARETTE SMOKING

The study of smoking histories in persons who have survived a clinical manifestation of coronary heart disease and in persons otherwise matched (by age, sex, etc.) but without clinical coronary heart disease has been performed by Gertler and White[28] and by Yater and co-workers[29]. The Gertler and White study was done on their series of 97 men who had had a myocardial infarction below the age of 40 years and who had survived the episode. A matched control group of men was also questioned by these workers with reference to smoking habits. While it was found that both the myocardial infarction survivors and the men of the matched control group had appreciable numbers of cigarette smokers amongst them, two facts became evident as a result of the questioning concerning cigarette smoking habits:

(1) The average number of cigarettes habitually smoked by the group of myocardial infarction survivors was approximately 50% higher than the average number of cigarettes habitually smoked per day by the matched control group.

(2) There were approximately twice as many non-smokers among the matched control men as there were in the group of survivors of myocardial infarction.

Yater and co-workers did a similar retrospective study in a series of men between 18 and 39 years of age who experienced a non-fatal myocardial infarction while serving in the U. S. Army. They contrasted the reported cigarette smoking history for this group with that for a matched control Army group of men. They found that amongst the myocardial infarction group 53% reported having smoked five or more cigarettes per day and for the matched control group 57% reported having smoked five or more cigarettes per day. However, a very striking difference was found when the groups were considered on the basis of having smoked *ten* or more cigarettes per day. There were 68% of the myocardial infarction group who reported smoking this much, whereas only 19% of the matched control group who reported smoking ten or more cigarettes per day.

The studies of Gertler and White and of Yater and co-workers are quite consistent with each other, both indicating

that heavy cigarette smoking was distinctly more frequent among the myocardial infarction cases than among their matched controls Within the limitations of this type of study involving retrospective questioning there appears from the evidence to exist an association between heavy cigarette smoking and subsequent coronary heart disease There are, however, good reasons why such evidence by itself can be regarded as inadequate to establish the relationship between cigarette smoking and coronary heart disease First there is the possibility that the answers given by the myocardial infarction patients may, in part have been influenced by their own suspicion that cigarette smoking had in some way contributed to their development of coronary heart disease Under such circumstances there would have existed a tendency for this group to overestimate the average number of cigarettes smoked Furthermore since such evidence arises primarily from the study of *survivors* of myocardial infarction there are missing from the series those persons who had not survived their myocardial infarction and who therefore were unable to provide answers concerning their smoking habits The possible influence of this deletion is difficult to assess

Thus the retrospective evidence while highly suggestive of an association between cigarette smoking and later clinical coronary heart disease is inconclusive A far more satisfactory approach is found in the *prospective* type of study where a determination is made of the smoking habits of a large number of persons preferably tens or hundreds of thousands at a time when they are overtly in health and free of evidence of clinical coronary heart disease Out of such a large series of persons in overt health there will with the passage of time grow a number of cases of *de novo* clinical coronary heart disease some surviving others not For *these* cases of clinical coronary heart disease the smoking history will have been known *in advance* of the clinical occurrence of coronary heart disease Such smoking histories can neither be influenced by survivorship from the clinical episode nor by any preconceived notions of the subjects with respect to the possible relationship of cigarette smoking with coronary heart disease In such a study the time required for a definitive answer is largely dependent upon the number of per

sons in the original large group under observation The larger the number of persons in overt health who are questioned concerning smoking habits the sooner will there be a sufficient number of episodes of clinical coronary heart disease so that an analysis can be made of possible relationships between cigarette smoking and the risk of clinical coronary heart disease Fortunately such a study has now been done on a very large scale by Hammond and Horn[6] of the American Cancer Society with highly conclusive results

In the American Cancer Society study field workers interviewed over 200 000 persons with respect to their smoking habits that is whether they had ever smoked if yes how much did they smoke and what (cigarettes cigars or pipes) and whether or not they quit smoking These findings were maintained on file and during the ensuing months and years a number of clinical episodes of coronary heart disease occurred in this very large population sample under study The early findings from this study were published by Hammond and Horn in 1954[67] The results showed clearly that men in their fifties and sixties who were regular smokers of cigarettes developed approximately 1½ to 2 times as many myocardial infarctions per thousand men per year as did those men who had never smoked cigarettes Such evidence derived by the questioning of a large sample of the population *first* and then observing *thereafter* who develops clinical coronary heart disease is free of all the criticisms that may be levelled at studies involving the questioning of men who have survived one or more episodes of clinical coronary heart disease The Cancer Society evidence hardly leaves room for doubt or question concerning the existence of a positive association between heavy cigarette smoking and an excessive incidence rate of clinical manifestations of coronary heart disease Yet consistently in certain quarters there has existed an intensive effort to belittle the significance of the highly important findings of Hammond and Horn

One common statement concerning these studies is that the proof of a higher incidence rate of clinical coronary heart disease in regular cigarette smokers than in non smokers does not *of itself* prove that cigarette smoking is a *cause* of clinical coronary

that heavy cigarette smoking was distinctly more frequent among the myocardial infarction cases than among their matched controls Within the limitations of this type of study involving retrospective questioning, there appears, from the evidence, to exist an association between heavy cigarette smoking and subsequent coronary heart disease There are however good reasons why such evidence by itself can be regarded as inadequate to establish the relationship between cigarette smoking and coronary heart disease First there is the possibility that the answers given by the myocardial infarction patients may in part have been influenced by their own suspicion that cigarette smoking had in some way contributed to their development of coronary heart disease Under such circumstances there would have existed a *tendency for this group to overestimate the average number of* cigarettes smoked Furthermore since such evidence arises primarily from the study of *survivors* of myocardial infarction there are missing from the series *those persons who had not survived* their myocardial infarction and who therefore were unable to provide answers concerning their smoking habits The possible influence of this deletion is difficult to assess

Thus, the retrospective evidence while highly suggestive of an association between cigarette smoking and later clinical coronary heart disease is inconclusive A far more satisfactory approach is found in the *prospective* type of study where a determination is made of the smoking habits of a large number of persons preferably tens or hundreds of thousands at a time when they are overtly in health and free of evidence of clinical coronary heart disease Out of such a large series of persons in overt health there will with the passage of time grow a number *of cases of de novo clinical coronary heart disease some* surviving others not For *these* cases of clinical coronary heart disease the smoking history will have been known *in advance* of the clinical occurrence of coronary heart disease Such smoking histories can neither be influenced by survivorship from the clinical episode nor by any preconceived notions of the subjects with respect to the possible relationship of cigarette smoking with coronary heart disease In such a study the time required for a definitive answer is largely dependent upon the number of per

THE BASIS FOR THE OBSERVED ASSOCIATION OF CIGARETTE SMOKING AND CORONARY HEART DISEASE

With the solidly established finding that cigarette smoking is positively associated with excessive coronary heart disease the prime question arises as to whether new or independent information is provided Either cigarette smoking becomes associated with excessive coronary heart disease via a relationship of cigarette smoking with one of the already established factors in coronary disease development or via some wholly new mechanism The only factors that still stand critical testing for provision of *independent* information about the risk of an individuals developing clinical coronary heart disease are

(1) The blood level of the S_f0 12 12 20 20 100 and 100-400 lipoproteins

(2) The diastolic blood pressure

It is therefore necessary to know whether cigarette smoking is or is not related to the level of any of these blood lipoproteins and whether or not it is related to the level of the diastolic blood presure If *no* such relationships exist then it would follow that cigarette smoking must be *independently* related to the development of clinical coronary heart disease and that the smoking history of an individual provides *additional* information concerning his risk of future clinical coronary heart disease If on the other hand demonstrable relationships exist between cigarette smoking and the blood lipoprotein levels or between cigarette smoking and the diastolic blood pressure or both it becomes necessary to determine whether such relationships account for part or all of the observed relationship between cigarette smoking and the incidence rate of clinical coronary heart disease

CIGARETTE SMOKING AND BLOOD LIPOPROTEIN LEVELS

Direct experimental data are now available for a large scale study of humans which provide the extent of relationship of cigarette smoking with lipoprotein levels and atherogenic index values The results were originally reported on 461 persons[69]

heart disease The reasoning behind such criticism is that possibly a certain type of individual is prone to develop clinical coronary heart disease and is (for reasons not given by the critics) the type of person who is likely to become a regular smoker of cigarettes If this be true it is argued the proneness to coronary heart disease might still exist even if such a person either had never taken up smoking or had quit smoking cigarettes No sound scientific thinker would deny the validity of this *possible* explanation of the observed findings Indeed such a possibility must always be considered in problems such as this one But it would be the height of folly to forget the *other* possibility, which is *at least* equally likely that cigarette smoking *is* one of the direct causes of an increased incidence rate of clinical coronary heart disease In scientific medical problems such as this one the demonstration of a positive association between two variables e g cigarette smoking and coronary heart disease incidence rate is an excellent *first* step Whether the first item (cigarette smoking) causes the second item (clinical coronary heart disease) or whether both items are separately caused by some third factor (cigarette smoking and coronary heart disease both being separate results of the metabolic makeup or personality makeup of the individual) can best be considered through appropriate further studies What is of prime importance is the realization that the clear-cut demonstration of a marked association between heavy cigarette smoking and subsequent clinical coronary heart disease is a monumental step forward in the elucidation of factors important in the development of coronary heart disease Even if it should develop that cigarette smoking is *not* an actual cause of coronary heart disease the information developed could not help but to lead to identification of *some* factor about smokers of cigarettes that leads them to show an inordinate average susceptibility to clinical coronary heart disease Valuable leads such as this one are not so easily found as to allow for casual or summary dismissal of their importance

TABLE XXXIX

Lipoprotein Levels and Atherogenic Index Values in Smokers and Non-Smokers

MEN (Category and Number of Men)	Mean S_f 0-12 mg/100 ml	Mean S_f 12-20 mg/100 ml	Mean S_f 20-100 mg/100 ml	Mean S_f 100-400 mg/100ml	Mean Atherogenic Index (units)	Average Number of Cigarettes Per Day
48? men who never smoked	33? 8	48 ?	81 7	49 5	66 ?	0
99 men who smoke fewer than 10 cigarettes per day	316	48 2	86 0	45 5	67 0	3 7
31? men who smoke 10-19 cigarettes per day	35? 2	47 1	91 7	0	?9 6	12 7
6?3 men who smoke more than ?0 cigarettes per day	3?? 5	50 ?	93 1	19 3	71 1	22 6
17 men who had given up cigarette smoking	? ? 7	47 ?	87 8	2 8	?6 8	0
1?6 men who smoked pipes or cigars or both but no cigarettes	33? 7	48 0	90 6	?9 6	68 4	0
WOMEN (Category and Number of Women)						
198 women who never smoked	303 0	3? 7	51 7	14 6	48 5	0
?? women who smoke fewer than 10 cigarettes per day	29? 9	30 7	?9 7	14 1	47 3	4 5
?? women who smoke between 10 and 19 cigarettes per day	318 8	3? 1	51 1	12 1	49 6	12 1
4? women who smoke more than ?0 cigarettes per day	? ?0	?? 4	17 7	10 ?	?9 ?	21 0
15 women who had given up cigarette smoking	?7	29 8	?? 6	13 0	13 ?	0

*Since the mean age of the various groups of men ranged from 32 6 to 3? ? years all values were adjusted to 3? 0 years Similarly for women all values were adjusted to 30 0 years

with extension and confirmation of the findings now in 2201 persons. *These individuals* were asked to fill out a questionnaire concerning their past and present smoking *habits* at the time they were undergoing a routine periodic medical examination at their place of employment. These persons had no idea of the purposes to which the questionnaire might be put nor were they aware of *other measurements being made for correlation* studies with the smoking history. It seems virtually certain that studies of the relationship of smoking habits with serum *lipoprotein levels* conducted *in this manner* could not conceivably been systematically biassed in one direction or another. In another part of this medical examination blood pressures were measured in a routine fashion and a sample of blood was withdrawn for lipoprotein and other biochemical analyses. The smoking *history questionnaire provided data adequate to subdivide* the entire population sample into those who never had smoked, those who smoked cigarettes (divided into sub-categories dependent upon the average number of cigarettes smoked per day), those who had been smokers of cigarettes but who had quit smoking, and those who smoked cigars and/or pipes but not cigarettes. The lipoprotein and atherogenic index findings for the various categories of smokers and for non-smokers are presented *in Table XXXIX. Cigarette smokers among the men* show highly significant elevations of S_f 0-12 and S_f 20-100 lipoproteins and of the atherogenic index in comparison with those men who never had smoked. Further the group smoking cigarettes heavily (20 or more per day) showed higher values of these variables than did those who smoked fewer than 20 cigarettes per day. These data establish conclusively that cigarette smoking is positively associated with elevation in Atherogenic *Index values and hence that at least part of the association of* cigarette smoking with a high incidence rate of coronary heart disease would be expected as a result of the cigarette smoking-atherogenic index *relationship. Quantitative* assessment *of how* large this part is will be made below.

It is of course not unexpected that there will be those who can say that these data do not *prove* that cigarette smoking *causes* the observed elevation in S_f 0-12 and S_f 20-100 lipoproteins

TABLE XXXIX

Lipoprotein Levels and Atherogenic Index Values in Smokers and Non Smokers

MEN (Category and Number of Men)	Mean S_f 0–12 mg/100 ml	Mean S_f 12–20 mg/100 ml	Mean S_f 20–100 mg/100 ml	Mean S_f 100–400 mg/100 ml	Mean Atherogenic Index (units)	Average Number of Cigarettes Per Day
486 men who never smoked	[illegible]36.8	48.6	81.7	49.5	66.9	0
99 men who smoke fewer than 10 cigarettes per day	31[illegible].7	48.[illegible]	86.0	43.3	67.0	3.7
315 men who smoke 10–19 cigarettes per day	3[illegible]2.2	47.1	91.7	[illegible]0.2	[illegible]9.6	1[illegible].7
6[illegible]3 men who smoke more than 20 cigarettes per day	3[illegible]1.5	[illegible]0.[illegible]	95.1	49.3	71.1	[illegible]6
217 men who had given up cigarette smoking	3[illegible]7	17.3	87.8	[illegible]2.8	6[illegible].8	0
1[illegible] men who smoked pipes or cigars or both but no cigarettes	33[illegible].7	48.0	90.6	59.6	68.4	0
WOMEN (Category and Number of Women)						
1[illegible]8 women who never smoked	303.0	3[illegible].7	51.7	14.6	48.5	0
33 women who smoke fewer than 10 cigarettes per day	99.9	30.7	19.7	14.1	47.3	4.[illegible]
[illegible]6 women who smoke between 10 and 19 cigarettes per day	318.8	3[illegible].1	[illegible]1.1	1[illegible].1	49.[illegible]	12.1
4[illegible] women who smoke more than 20 cigarettes per day	32[illegible].0	39.1	17.7	10.[illegible]	49.3	[illegible]1.0
13 women who had given up cigarette smoking	[illegible]75.7	[illegible]9.8	1[illegible]	13.0	43.9	0

Since the mean age of the various groups of men ranged from 32.6 to [illegible] years all values were adjusted to [illegible] years. Similarly for women all values were adjusted to 30.0 years.

and in atherogenic index value To be sure there does exist the *possibility* that persons of certain metabolic types or personality types may smoke more cigarettes than others and may show higher atherogenic index values than others and that the observed association of cigarette smoking with atherogenic index simply reflects such personality and metabolic types But the existence of this as a *possibility* does not make it the *reality* hoped for by some for it is at least equally likely (and from additional evi dence much more than equally likely) that cigarette smoking *causes* the observed elevation in S_f0 12 and S_f20 100 lipoproteins

FILTER TIP CIGARETTES VERSUS REGULAR CIGARETTES

The tobacco industry has put a great deal of effort into a campaign to induce cigarette smokers to switch to filter tip cig arettes There can be little doubt but that the individual smoker who chooses a filter tip cigarette is influenced to do so by his hope that any potentially adverse effects of cigarette smoking upon health may be mitigated through the use of filter tip cig arettes It is of interest, therefore to know whether or not filtering smoke through the commonly available filter tip cig arettes alters in any way the association of cigarette smoking with serum lipoprotein and atherogenic index values The ques ionnaires utilized in the above described study specifically requested information concerning the brand of cigarette smoked and whether or not the cigarette was of a filter tip type For purposes of analysis all non filtered brands are considered here as one group all filtered brands as another group While this does not allow comparison of possible efficiency of one filter tip with another it does provide a measure of the effect of filtra tion in the form utilized by a reasonable cross section of cigarette smokers The comparison data are presented in Table XL No significant differences in lipoprotein levels or atherogenic index values can be demonstrated between those cigarette smokers using the usual group of filter tip cigarettes and those using the unfil tered brands With respect to that part of the association of cigarette smoking and coronary heart disease that arises through the association of cigarette smoking with Atherogenic Index val

TABLE XL

SERUM LIPOPROTEIN LEVELS AND ATHEROGENIC INDEX VALUES IN SMOKERS OF FILTER TIP CIGARETTES VERSUS SMOKERS OF REGULAR (NON FILTERED) CIGARETTES

Category	*Mean S_f0 12 mg/100ml*	*Mean S_f12 20 mg/100ml*	*Mean S_f0 100 mg/100ml*	*Mean S_f100 400 mg/100ml*	*Mean Atherogenic Index (units)*	*Mean Number of Cigarettes Per Day*
[illegible]4 *men who smoked filter tip* cigarettes	364 4	48 8	93 6	51.2	70 9	18.2
833 *men who smoked regular* (non filtered) cigarettes	365 6	50 8	91 [illegible]	49 1	70 6	18 0

The *question concerning filtration* was introduced into the latter half of this study Hence data are available only for 1087 men for this feature No conceivable bias was introduced by this.

ues no amelioration of the situation is achieved by a substitution *of the filter tip cigarettes in common use during the 1954 1957* period when this study was done

PIPE AND CIGAR SMOKING AND SERUM LIPOPROTEINS

Hammond and Horn s report on the association of smoking with coronary heart disease showed a much more striking effect for cigarette smoking than for cigar and pipe smoking although a low degree of association could be demonstrated for cigar and pipe smoking The data of Table XXXIX indicate that no significant elevation of any of the lipoproteins or of the atherogenic index was demonstrable *in those who smoked cigars and/or pipes* but who never had smoked cigarettes Some possible explanations of the lack of an effect of the use of tobacco in these forms are (1) a lesser consumption of tobacco in pipe or cigar *smokers than in cigarette smokers (2) a temperature difference* in the burning of tobacco in the various forms or (3) an influence of some component of cigarettes other than the tobacco itself

REVERSIBILITY OF THE EFFECT OF CIGARETTE SMOKING UPON SERUM LIPOPROTEIN LEVELS

Many of the individuals examined in this study had at one time been smokers of cigarettes but had for a variety of reasons made the decision to quit smoking Some had quit as recently as a few weeks before the questionnaire and blood sampling others as long as 10 years before An analysis was made of the lipoprotein levels of this entire group of 217 quitters of cigarette smoking in comparison with those who never had smoked cigarettes The data are presented in Table XXXIX No significant difference in level of any of the four classes of lipoproteins or of the atherogenic index can be demonstrated to exist between the group who had quit cigarette smoking and the group who *had never smoked cigarettes* If it is assumed that while the members of the first group *had* smoked cigarettes they would have shown the elevation in lipoprotein levels characteristic of

current cigarette smokers it follows that cessation of cigarette smoking has resulted in a *reduction* in lipoprotein and Athero genic Index values This would indicate that *whatever* the mechanism is by which cigarette smoking becomes related to ele vation of blood lipoprotein levels it is possible to overcome such elevation by cessation of smoking

The possibility exists of course that the quitters of cig arettes represent a special group of persons among the smokers and that the very fact that they quit smoking proves this The argument could be advanced that possibly *these* cigarette smokers never had had the lipoprotein elevation characteristic of cigarette smokers and hence that the absence of an elevation in quitters does not prove *reversibility* of an effect of cigarettes on serum lipoproteins Such requirements of special types of persons first to explain the lipoprotein elevation in cigarette smokers and next to explain the effect of cessation of smoking begin to multiply the number of metabolic or personality make ups required and render such *possible* explanations of all the findings very remote in comparison with the more plausible one that cigarette smoking is a causative agent in lipoprotein eleva tion and that hence removal of the causative influence removes the effect as has been experimentally observed

CIGARETTE SMOKING AND BLOOD PRESSURE LEVELS

Physiologists and pharmacologists have long been interested in the possible influence of tobacco and some of its chemical constituents upon such vital measurements as the blood pressure level Many of the studies that have been reported have focussed upon the relatively acute effects of smoking upon the blood pressure Such information is extremely useful but needs supplementation by studies of possible chronic effects of cig arette smoking upon the habitual blood pressure of individuals

In direct investigations of the acute effect of cigarette smok ing upon the diastolic blood pressure level of habitual smokers Roth[69] found that her subjects showed an average rise in diastolic pressure of 11 mm Hg above a baseline average value of 69 mm Hg during the actual act of smoking two regular cigarettes con

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sustained effect of habitual cigarette smoking upon blood pressure level exists

QUANTITATIVE EVALUATION OF THE RELATIONSHIP OF CIGARETTE SMOKING WITH INCIDENCE RATE OF CLINICAL CORONARY HEART DISEASE

The objective of determination of the presence or absence of an intrinsic independent effect of cigarette smoking per se upon coronary heart disease can now be realized First it is necessary to assess what part of the overall effect can be explained both through the association of cigarette smoking with atherogenic index values and through that of cigarette smoking with blood pressure levels The statistical calculations of Hammond and Horn[70] showed that regular smokers of 40 cigarettes per day (2 packs) show approximately 2 2 times as high an incidence rate of clinical coronary heart disease as do non smokers From the direct measurements of the relationship of cigarette smoking with lipoprotein level and atherogenic index values smokers of 40 cigarettes per day experience an average elevation in Atherogenic Index value of 8 3 units For men in the 40 59 year age bracket this would mean an Atherogenic Index value of approximately 83 8 units for smokers of 40 cigarettes per day contrasted with a value of 75 5 units for non-smokers Reference to Table XVI (Chapter V) indicates that the relative incidence rate of coronary heart disease for these atherogenic index values is 4 82/3 34 or a 1 44 fold increase in coronary heart disease incidence rate for smokers of 40 cigarettes per day compared with that for non smokers But this *is the increase* in expected incidence rate taking into account only the association of cigarette smoking with atherogenic index Complete evaluation of the expected incidence rate in smokers *requires* also an accounting of the blood pressure effect

Since the data described above show *no sustained* effect of cigarette smoking upon diastolic blood pressure level the considerations need to deal only *with the* acute effects of cigarette smoking upon the diastolic blood pressure In the chapter of this book (Chapter VII) where the relationship of age with

secutively However, within approximately five minutes the diastolic pressure level had returned to the pre smoking base line value Therefore, *it is clear that while smoking the average* cigarette smoker does experience a rise in diastolic blood pressure but the effect wears off very rapidly following the actual act of smoking

The rapid decay of the effect of smoking cigarettes upon the blood pressure does not preclude the possibility that habitual smoking of cigarettes may produce some sustained rise in diastolic blood pressure However, direct studies of this question reported below, indicate that no such sustained effect upon blood pressure is demonstrable This was shown in the same group of 2201 consecutive employed persons who were questioned concerning smoking habits and whose lipoprotein levels were measured The data relating blood pressure values to various categories of smoking habits are presented in Table XLI Since the blood pressure measurements in this study were made at least 15 minutes after the act of smoking a cigarette in those who may have smoked prior to the medical examination the type of acute effect found by Roth should not have influenced these observations The absence of any demonstrable deviation in the mean diastolic blood pressure for habitual cigarette smokers contrasted with persons who had never smoked indicates that no

TABLE XLI

DIASTOLIC BLOOD PRESSURE LEVELS IN SMOKERS AND NON SMOKERS*

Category	*Mean Diastolic Pressure*** *(mm Hg)*
486 men who never smoked	71 3
99 men who smoke fewer than 10 cigarettes per day	71 3
315 men who smoke 10 to 19 cigarettes per day	70 6
673 men who smoke more than 20 cigarettes per day	70 6
217 men who had given up cigarette smoking	70 7
126 men who smoked pipes or cigars or both but no cigarettes	70 3

* The values of mean diastolic pressure were all corrected by the very small correction necessary to adjust to 35 0 years of age for all groups

** These pressures were taken reclining a minimum of 15 minutes after the last cigarette was smoked if the examinee smoked at all

This means that the combined effect of elevation of atherogenic index and diastolic blood pressure leads to the prediction of a 1 8 fold incidence rate of clinical coronary heart disease in smokers of 40 cigarettes per day in comparison with non smokers This is to be compared with the 2 2 fold incidence rate actually observed by Hammond and Horn It appears quite clear that the effect of cigarette smoking on coronary heart disease incidence rate is wholly or nearly wholly explained by the elevation in atherogenic index and diastolic blood pressure in cigarette smokers There cannot be much residual independent status of cigarette smoking beyond these mechanisms

Those who have quit cigarette smoking show a coronary disease incidence rate between those of smokers and non smokers[9] The lipoprotein findings plus the accumulation concept for coronary disease risk predict precisely this result if reversibility of *established* risk is not complete

coronary heart disease incidence rate was discussed it was pointed out that all the available evidence indicates that the blood pressure operates as an *accumulative* factor over time rather than as an *instantaneous factor* Thus a particular elevation of blood pressure operating over two years would accumulate twice as much toward the risk of ultimate clinical coronary heart disease as would that same elevation in pressure operating over one year In the absence of any information to the contrary, the most reasonable approximation to the effect of blood pressure elevation for much shorter intervals of time is to consider an accumulation proportional to the time interval involved Thus in this case the knowledge exists from Roth s data[69] that the mean diastolic blood pressure is elevated 14 mm Hg during cigarette smoking The average duration of this effect is approximately 10 minutes per cigarette Therefore, a person who smokes 40 cigarettes per day would show such a blood pressure elevation for 40x10 or 400 minutes per day or about 7 hours per day out of every 24 hours An elevation of diastolic blood pressure of 14 mm Hg for 7 hours out of 24 hours would correspond to an average elevation of pressure of 7/24 of 14 or 4 1 mm Hg spread over each day This is the average increase in diastolic blood pressure that can be used to estimate the increase in coronary heart disease incidence rate resulting from the association of acute blood pressure rises with cigarette smoking The average blood pressure of 40 59 year old men is 74 7 mm Hg and with a 4 1 mm rise the cigarette smokers would show an average pressure of 78 8 mm Hg From Table XIV (Chapter V) this rise in diastolic blood pressure corresponds to a 3 94/3 16 or 1 25 fold increase in coronary heart disease incidence rate which is the increased incidence rate anticipated for smokers of 40 cigarettes per day as compared with non smokers

The *overall* comparison of the coronary heart disease incidence rate for smokers of 40 cigarettes per day and for non smokers is determined by multiplying the increased incidence rate due to the atherogenic index effect by that for the diastolic blood pressure effect Therefore the factor of 1 44 (for the atherogenic index effect) is to be multiplied by 1 25 (for the diastolic blood pressure effect) giving an overall factor of 1 80

the extent to which diabetes mellitus might predispose to excessive coronary heart disease today it would be a matter of some urgency to know with what kind of people these past reports have been dealing It is no less important to know today when one discusses diabetics with what type of people one is dealing Unfortunately so many of the impressions concerning diabetes mellitus arise either from hospital statistics or clinical statistics that it is extremely difficult to know accurately the incidence of such complications as coronary heart disease in the diabetic population as a whole rather than in some select part of the diabetic population which finds itself going to a clinic or a hospital This very fact alone may bias the data such as to lead to an erroneous impression concerning complications of the diabetic state A variety of complaints may ultimately lead a person with a disease such as diabetes mellitus to seek care in a medical clinic one of which complaints might be angina pectoris or other manifest coronary heart disease Hence the analysis of hospital statistics or clinic statistics with respect to the incidence of coronary heart disease in diabetes mellitus may be grossly misleading as an index to the status of diabetics in the population at large Perhaps the most effective way to start consideration of this problem is to look back at the pre insulin period In the pre insulin period we had what might be called essentially a homogeneous population of diabetics at least with respect to the one fact that none of them were being treated with insulin which can no longer be said at the present time During that period it appears reasonably certain that coronary heart disease and sequelae of arteriosclerosis in other vascular beds was more frequent in the diabetic subjects than in the population at large Even during *that period* the estimate of the frequency of such disease in the diabetics must have been biassed by the fact that certainly the more severe cases and those with complications most readily found their way into the hospital and clinic populations from which coronary disease statistics were derived for the diabetic Still for the untreated diabetic during the pre insulin period we can look at some of the scientific clinical evidence concerning such patients to determine what might have been expected then with respect to coronary heart disease

Chapter XII

THE RELATIONSHIP OF DIABETES MELLITUS WITH CORONARY HEART DISEASE

THE OPINION is still widely held in medical circles that diabetes mellitus is a disorder characterized by an excessive incidence of premature coronary heart disease Indeed it has often been stated by medical authorities that since diabetes mellitus *itself need no longer be a fatal disease because of the use of* insulin or some of the recent substitutes for insulin therapy, the diabetic now dies of the complications of arteriosclerosis among which coronary heart disease is prominent The crucial question *at hand is 'To what extent does the diabetic die of coronary heart* disease earlier in life than does any member of the population at large? If the diabetic is protected against death from diabetic acidosis and coma and therefore becomes essentially a member *of the population at large (but with diabetes) one could* antici pate that coronary heart disease may be at least as frequent among diabetics as it would be among other members of the population Since coronary heart disease occurs so frequently in the popula *tion at large it is not surprising that physicians should run into* many diabetics who develop coronary disease ultimately includ ing between ¼ and ½ of them But if this frequency of heart disease is no greater in diabetics than in the population at large, then the *impression that diabetes mellitus is a predisposing* factor *as of today,* might be erroneous

Oft quoted in support of the concept of the excessive fre quency of coronary heart disease in diabetes mellitus are data published *in the literature between 1930 and 1950* and based upon the consideration of persons who were in their sixties and seventies during that period Before reaching a conclusion as to

the extent to which diabetes mellitus might predispose to excessive coronary heart disease today it would be a matter of some urgency to know with what kind of people these past reports have been dealing It is no less important to know today when one discusses diabetics with what type of people one is dealing Unfortunately so many of the impressions concerning diabetes mellitus arise either from hospital statistics or clinical statistics that it is extremely difficult to know accurately the incidence of such complications as coronary heart disease in the diabetic population as a whole rather than in some select part of the diabetic population which finds itself going to a clinic or a hospital This very fact alone may bias the data such as to lead to an erroneous impression concerning complications of the diabetic state A variety of complaints may ultimately lead a person with a disease such as diabetes mellitus to seek care in a medical clinic one of which complaints might be angina pectoris or other manifest coronary heart disease Hence the analysis of hospital statistics or clinic statistics with respect to the incidence of coronary heart disease in diabetes mellitus may be grossly misleading as an index to the status of diabetics in the population at large Perhaps the most effective way to start consideration of this problem is to look back at the pre insulin period In the pre insulin period we had what might be called essentially a homogeneous population of diabetics at least with respect to the one fact that none of them were being treated with insulin which can no longer be said at the present time During that period it appears reasonably certain that coronary heart disease and sequelae of arteriosclerosis in other vascular beds was more frequent in the diabetic subjects than in the population at large Even during that period the estimate of the frequency of such disease in the diabetics must have been biassed by the fact that certainly the more severe cases and those with complications most readily found their way into the hospital and clinic populations from which coronary disease statistics were derived for the diabetic Still for the untreated diabetic during the pre insulin period we can look at some of the scientific clinical evidence concerning such patients to determine what might have been expected then with respect to coronary heart disease

During the pre insulin period the availability of therapy other than dietary therapy was essentially non existent and during that same period uncontrolled diabetes can be said to have been rampant To be sure the obese middle aged diabetic during that period was in essence no different from the obese middle aged diabetic of today We do know that in such cases of diabetes that the correction of diet and of attendant over weight will in many cases lead to an amelioration of the diabetic state a reduction in or elimination of glycosuria a reduction in hyperglycemia and clinical well being wholly without the use of insulin However there were many diabetics in whom this favorable set of changes could not be induced by dietetic therapy alone during the period in which insulin was absent from the scene The occurrence of episodes of severe acidosis and even of coma was a frequent occurrence with a large number of diabetics dying during such episodes Diabetic acidosis of severe degree and diabetic coma still occur today although much more infrequently than before but nevertheless their occurrence provides us with a direct way of observing the type of phenomenon that must have been extremely common during the pre insulin period Among the most startling findings in uncontrolled diabetes in acidosis or in coma are those which center around the alterations of blood lipid transport Indeed it can be stated that no other disease has yet been observed which is capable of producing within a matter of days the massive changes in blood lipid transport that can be observed as a diabetic patient passes from control into decontrol and acidosis and conversely as a diabetic in coma or acidosis is once more brought under control These considerations can best start with the diabetic in severe decontrol and acidosis with or without coma Numbers of these patients have been studied with respect to the lipoprotein levels of the various classes involved in coronary heart disease such as the S_f0 12 S_f12 20 S_f20 100 and S_f100-400 classes during the phase of severe diabetic acidosis and decontrol and during the phases of return to control[71 ^]

The average patient under these circumstances is characterized by a very very marked derangement of blood lipoprotein transport which involves a lowering of the S_f0 12 lipoproteins

TABLE XLII

S UM LIPOPROTEIN LEVELS IN DIABETIC ACIDOSIS AND COMA

Case	Age (years)	Sex	Clinical State	S_f 0-12 mg/100 ml	S_f 12-20 mg/100ml	S_f 20-100 mg/100ml	S_f 100-400 mg/100 ml	Atherogenic Index (units)
1	37	F	Marked Acidosis No coma Cutaneous Xanthomata	195	155	11 0	389	897
	44	F	Acidosis and Coma	17	65	343	383	1.6
3	5.	F	Acidosis No coma Cutaneous Xanthomata	35	54	1082	16 2	506
4	1	M	Acidosis Semicoma	4	9	334	86	-19
5	11	F	Acidosis Semi coma	0	0	416	100	1J
6	1	F	Acidosis No coma	1 9	81	6 6	647	260
7	39	F	Acidosis Coma	409	139	264	n	1C2
8	35	M	Acidosis Semi coma	101	40	20		?
9	2	F	Acidosis No coma	3 6	105	164	2	95
10	13	F	Acidosis No coma	22(	91	105	31	63
			Grand Mean for 10 cases	2 4 6	74.2	450 4	835 7	260.5

accompanied by a massive elevation of the lipoproteins of higher flotation classes including those of the S_f 20-100 class the S_f 100-400 class and lipoproteins of even higher classes all the way out to those known as chylomicrons In Table XLII are presented the initial findings available for a series of diabetics who were *in the hospital in severe acidosis with or without coma* It can be noted that 7 out of 10 of these patients showed a marked derangement in lipoprotein transport of the type just characterized The mean values of the four lipoprotein classes for all ten cases shows the marked depression in S_f 0-12 lipoproteins and the massive elevation of the S_f 20-100 and S_f 100-400 lipoprotein classes While every diabetic in acidosis does not show a marked derangement of lipoprotein levels, the averages and the distribution of values speak for themselves with respect to the tremendous derangement that can be said to characterize the usual state of diabetic acidosis and severe diabetic decontrol The average *Atherogenic Index value of 260 5 units is between 3 and 4* times the average for adult males or females in the population at large Hence, with respect to the *rate of accumulation* of subclinical coronary heart disease (in all probability in the form of an increment in narrowing of the coronary arteries) it can be expected that the average diabetic in the state of acidosis is accumulating sub-clinical coronary heart disease at a phenomenal rate During the pre insulin period many diabetics probably could not have chronically been this far out of control but undoubtedly many of them must have been oscillated into and out of states approaching this degree of decontrol It would be anticipated that during such phases of decontrol they were developing an extensive degree of sub-clinical coronary heart disease It is not necessary for diabetics to be in a state of coma or semi coma in order to show the marked derangement in lipoprotein levels which accompanies severe diabetic decontrol Illustrative changes in lipoprotein levels for one patient followed carefully during her hospital stay while the diabetes was being brought under control are presented in Table XLIII

A most interesting sequence of events is observed during the period of days, weeks and months during which the diabetic patient has been brought under control from the state of severe

TABLE XLIII

SERIAL LIPOPROTEIN STUDIES DURING THE THERAPY OF DIABETIC ACIDOSIS IN A 37 YEAR OLD PATIENT

Day After Hospital Admission	Clinical State	S_f 0-12 mg/100 ml	S_f 12-20 mg/100ml	S_f 20-100 mg/100ml	S_f 100-400 mg/100ml	Atherogenic Index (units)
0	In acidosis and coma	195	155	11.0	3739	897
4th day	Out of acidosis	441	352	1912	1550	714
9th day	In diabetic control	444	428	1247	685	493
14th day	In diabetic control	939	338	670	139	295
29th day	In diabetic control	614	131	493	228	211
43rd day	In diabetic control	531	148	432	152	178
70th day	In diabetic control	616	150	332	159	173
56th day	In diabetic control	549	108	1 0	31	105
—Discharged from hospital—						
116th day	Supposedly in diabetic control at home but showing acetonuria	452	237	988	461	340
400th day	Supposedly in diabetic control at home but showing acetonuria	276	188	968	840	377

diabetic acidosis As the diabetes is brought under control through usual medical measures including insulin among others the massively elevated levels of lipoproteins above S_f400 and of the S_f100-400 class are noted to decline as a very early phenomenon During the time when the levels of these lipoproteins are falling, there is first a rise in concentration of those of successively lower flotation classes Thus as the S_f100-400 lipoprotein levels start falling the S_f20 100 lipoprotein levels show a rise in concentration, as though there might actually be a transformation occurring from the lipoproteins of the higher flotation classes to those of successively lower flotation classes With the passage of a little more time measured in days the S_f100-400 lipoprotein levels fall still further and then the S_f20 100 lipoprotein levels which at first were rising begin to decline accompanied first by an increase in the S_f12 20 lipoproteins and finally also in the S_f0 12 lipioproteins Still further along in this entire evolutions of events the S_f20 100 and S_f100-400 lipoproteins may approach values of the order of these observed in the population at large (even lower than for many persons in the population at large) At this time the S_f0 12 lipoprotein levels are massively elevated in comparison with the levels encountered in the members of the population at large Finally with further maintenance of diabetic control the massive elevation of the S_f0 12 lipoprotein levels recedes leaving the diabetic ultimately with the type of pattern that characterizes him or her during a state of control The lipoprotein distribution in diabetic control is not a standard one since there is variability among diabetics in control just as there is variability in the levels of the various lipoprotein classes among the members of the population at large All the events described above have been observed in several diabetic patients going from the stage of severe acidosis and decontrol back to control so that it is by no means the happenstance of a single particular diabetic patient This sequence of changes can be regarded as a general trend which characterizes diabetes during these stages Furthermore certain patients who have been brought out of severe acidosis have been observed for a period of months and years while attempting to control their diabetes at home The patient described in Table XLIII was observed

during a repeat episode of acidosis (although clinically a much milder episode of acidosis than during the initial study) During this second relatively mild episode of acidosis the patient showed a reversion to a lipoprotein distribution intermediary between that observed in the earlier marked decontrol stage and that in the stage of control during her hospital stay This general train of events can be anticipated to have been extremely common during the period before the introduction of insulin even though lipoprotein values were not available during that time to delineate the changes

That a disease process such as the accumulation of sub clinical coronary heart disease was in all probability going on excessively during such a period is supported by auxiliary (though not necessary) evidence concerning the development of xanthomatosis in the diabetic patient Xanthoma diabeticorum which is more commonly referred to as *eruptive* xanthoma diabeticorum is a lesion occurring in the skin histopathologically closely akin to the arterioatherosclerotic lesions of the coronary artery and of other medium and large arteries There are pathologists who would claim the ability to distinguish a xanthomatotic lesion from an athero arteriosclerotic lesion even though both lesions are grossly similar One might question the ability to make this distinction if the surrounding landmarks of tissue such as the coats of the vessel in the case of the arteriosclerotic lesion or the over lying skin in the case of the skin lesion were stripped away leaving the bare lesion Under these circumstances it can be fairly well assured that pathological differentiation of the lesions would be much less readily made There are abundant reasons to consider that the pathogenesis of these two lesions is extremely similar Diabetic patients do not commonly show the lesion of eruptive xanthoma diabeticorum during diabetic control Indeed the very term eruptive indicates the relatively acute onset of develop ment of such lesions and the acute nature of the entire process These lesions erupt during some aspect of the phase of severe diabetic decontrol and acidosis and may persist and increase dur ing the stage of marked diabetic acidosis and coma It is to be noted that such lesions occur in those cases who have enormously elevated lipoprotein levels of the S_f12-400 class as part of their

manifestation of the entire phenomenon of diabetic acidosis and decontrol There is very little doubt that the massively elevated lipoprotein levels of these classes are directly associated with the development of the eruptive xanthoma diabeticorum Furthermore, as the diabetic is brought back into control and out of acidosis and as the lipoprotein levels recede toward much more normal levels the lesions of xanthoma diabeticorum no longer develop de novo Old lesions which had appeared during the *stage of massive lipoprotein elevation begin to decrease in size* and in a period of weeks and months trailing the lipoprotein level lowering the lesions generally disappear completely leaving in most areas very little if any trace of the xanthomata This xanthomatous lesion which develops in association with extremely high lipoprotein levels is a manifestation of what can happen in the skin if lipoprotein levels are high enough For a process such as this it appears unquestionable from a variety of types of evidence that certain regions of the body differ with respect to receptivity to formation of the lipid filled lesions of this character It is not surprising, therefore to find that skin may be one of the less receptive areas as compared with tissues in general such as arterial walls and that the lesions which are seen in the skin form only when the lipoprotein levels are massively elevated There is no reason to consider that the lipoproteins are different in kind from those which exist at lower levels in the population at large but rather that they are so massively elevated in concentration during the state of diabetic acidosis that the skin lesions form The corresponding arterial lesions we can feel quite certain form at much much lower lipoprotein levels in the blood since arteriosclerosis proceeds at a fair rate in the population at large with more moderate lipoprotein levels

Thus during a phase of diabetic decontrol and acidosis with its massive elevation of lipoprotein levels it can be anticipated that, whatever rate of coronary atheroma development usually existed in such an individual it will have been massively accelerated during the periods of decontrol with the fabulous rises in lipoprotein levels which accompany such periods The diabetic during the pre insulin period must have been in and out of phases of severe acidosis and may have been midly acidotic for

very long periods of time since full control of the diabetes was not possible in that era without the assistance from insulin therapy Therefore regression of arteriosclerotic lesions that might have occurred (analogous to the regression of the xanthomatous lesions which occurs when the lipoproteins are lowered in an acidotic diabetic) may have been inhibited because of the maintenance of mild acidosis From studies of other xanthomatoses such as xanthoma tuberosum it is known (see Chapter X) that the longer standing lesions are no longer primarily the lipid laden lesions but instead have accumulated a considerable amount of fibrous tissue During the regression of such longer standing lesions in xanthoma tuberosum which accompanies lowering of lipoprotein levels the lipid element of the lesion regresses very markedly and may disappear entirely but the fibrous element does not To what extent the fibrotic element in the arteriosclerotic lesion develops more rapidly or less rapidly than in the xanthomatotic lesion cannot be stated but it is certain to develop at some reasonably comparable pace Therefore for the diabetic who has spent a fair part of his life in the acidotic state or decontrol state there will be expected with each deposition of lipid in arterial lesions a development of fibrosis and hence some accumulation of a partially or wholly irreversible part of the lesion even though the diabetes has been brought under control by medical measures

The entire discussion of the xanthomatosis of diabetes its relationship with the arteriosclerotic lesion and the relationship of both of these with the progression of sub-clinical coronary heart disease in patients with diabetes is *ancillary* evidence As stated earlier in this book because of controversies concerning the primacy of events in the development of the arteriosclerotic lesion evidence pertaining to arteriosclerosis would not be utilized as basic support for demonstration of the factors involved in the development of sub-clinical and clinical coronary heart disease However where ancillary evidence deriving from pathology might help understand a particular issue such ancillary evidence should not be neglected In this case there exists no need to utilize the ancillary evidence as the basic proof or evidence for the phenomenon at hand but it does lend further consistency to

manifestation of the entire phenomenon of diabetic acidosis and decontrol There is very little doubt that the massively elevated lipoprotein levels of these classes are directly associated with the development of the eruptive xanthoma diabeticorum Furthermore as the diabetic is brought back into control and out of acidosis, and as the lipoprotein levels recede toward much more normal levels, the lesions of xanthoma diabeticorum no longer develop de novo Old lesions which had appeared during the stage of massive lipoprotein elevation begin to decrease in size and in a period of weeks and months trailing the lipoprotein level lowering the lesions generally disappear completely, leaving in most areas very little if any trace of the xanthomata This xanthomatous lesion which develops in association with extremely high lipoprotein levels is a manifestation of what can happen in the skin if lipoprotein levels are high enough For a process such as this it appears unquestionable from a variety of types of evidence that certain regions of the body differ with respect to receptivity to formation of the lipid filled lesions of this character It is not surprising therefore to find that skin may be one of the less receptive areas as compared with tissues in general such as arterial walls and that the lesions which are seen in the skin form only when the lipoprotein levels are massively elevated There is no reason to consider that the lipoproteins are different in kind from those which exist at lower levels in the population at large, but rather that they are so massively elevated in concentration during the state of diabetic acidosis that the skin lesions form The corresponding arterial lesions we can feel quite certain form at much much lower lipoprotein levels in the blood since arteriosclerosis proceeds at a fair rate in the population at large with more moderate lipoprotein levels

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showing effects upon their coronary heart disease risk due to the time they spent as diabetics during the pre insulin period This point is commonly overlooked by authors writing in the 1940 s and 1950 s especially concerning diabetics in the seventh eighth and ninth decade of life and their incidence of coronary and other vascular disease Such evidence can hardly be utilized to provide the requisite information concerning the fate of diabetes of today under good control Therefore it is necessary to reeval uate completely for the diabetic of the present era what the real situation is with respect to the incidence of coronary heart disease

THE INCIDENCE OF CORONARY HEART DISEASE IN DIABETES MELLITUS IN THE POST INSULIN PERIOD

Ideally the determination of any possible increase in inci dence rate of clinical coronary heart disease in diabetics during the post insulin period would require the following evaluations

(1) The real incidence of diabetes mellitus in the population at large at various ages and for both sexes
(2) Follow up observations of an adequately large series of such diabetics random in the population at large to determine the age specific incidence rate of clinical coronary heart disease for both sexes
(3) Follow up of an adequately large sample of the non-diabetic population at large to determine the age specific incidence rate of clinical coronary heart disease in both sexes
(4) Assurance that the diabetic persons had not spent a large share of their life in the pre insulin era This would not be a serious problem in data collected now although it certainly has been in literature reports of the past few decades

What is available now in the way of evidence falls short by a tremendous margin of such evaluations The pitfalls of utiliza tion of clinic or hospital patients or of hospital autopsy data are many and have been alluded to in the earlier discussion above Thus comparison of the frequency of occurrence of diabetes mellitus in a hospital series of myocardial infarctions with the prevalence of diabetes in an age and sex matched sample of the

the concepts involved All the evidence concerning diabetic acidosis is self sufficient in terms of the direct relationship of blood lipoproteins to the development of sub clinical coronary heart disease without the intermediacy of the arteriosclerotic or xanthomatotic lesions Since it has been shown before (see Chapter V) that the higher the lipoprotein level the greater is the accumulation rate of sub-clinical coronary disease and hence *the greater ultimate risk of clinical coronary disease* it can be stated that a diabetic in acidosis, with the lipoprotein levels which characterize that state would have been accumulating sub clinical coronary heart disease at a tremendously increased rate in comparison with the diabetic in control or with the non diabetic Hence the frequent existence of severe decontrol of diabetes during the pre insulin period should have markedly increased the predisposition of diabetic patients to the development of early and severe coronary heart disease This is completely consistent with the numerous literature reports of a high incidence of coronary heart disease in the pre insulin period *However the pre insulin period is over* Indeed we are in a phase now where insulin itself is being compared with numerous other drugs that may replace it in part at least in the management of certain diabetic patients All the considerations of coronary heart disease incidence rate for the pre insulin period with its high frequency of acidosis and coma are of very little moment for the present era The crucial question is whether or not diabetes as it is usually encountered today is still characterized by any excessive frequency of coronary heart disease In order to assess this issue critically several points must be carefully considered First when statistical data concerning the incidence of coronary heart disease in diabetic patients between 1930 and 1950 are reviewed it must be remembered that many of such diabetics (especially those in the older age groups) must have spent a *considerable portion of their life in the pre insulin* period or in the early insulin period when insulin was not as widely used as it has been in more recent years Hence if at least *part* of *the accumulation of sub-clinical coronary heart disease* is not reversible it would be expected that some of the diabetics of the 1930 1950 era especially those of older age groups would still be

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(3) Follow up of an adequately large sample of the *non* diabetic population at large to determine the age *specific incidence* rate of clinical coronary heart disease in both sexes
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non diabetic population can be seriously biassed For example a hospital with a well known and well managed diabetes clinic service is likely to have a higher proportion of diabetics in its overall clientele than characterizes the incidence of diabetes mellitus in the population at large In such a clinic there will exist a high index of awareness of coronary heart disease among their diabetics *This together with the loading of the overall clientele* with diabetics will tend to produce a falsely high incidence of diabetes mellitus in a myocardial infarction series from such a hospital if that incidence of diabetes is compared with the incidence of diabetes in the population at large Similarly if a hospital draws upon one group ethnically or on some other basis, the incidence of diabetes in a myocardial infarction series cannot *and should not be justifiably compared with that in the population* at large It has been stated in the literature [3] that Jews show a higher prevalence of diabetes mellitus than that for the non Jewish population If this be true, it is completely inappropriate to relate the incidence of diabetes in a series of myocardial infarction cases from a Jewish hospital with the incidence of diabetes mellitus in the overall population at large

A survey of the literature (even avoiding those reports contaminated by diabetics from the pre insulin period) reveals that the possibilities for bias are large and unfortunately subtle enough that efforts to correct for such bias are not particularly fruitful

However even with whatever bias exists in the literature reports from clinics and hospitals it is not unreasonable to try to establish some upper limits to any excessive predisposition of diabetic persons to develop clinical coronary heart disease utilizing such literature data The nature of the biassing errors are in general such as to *overestimate* any excessive risk for diabetics *rather than to underestimate it* Wright et al, Master et al Doscher and Poindexter and Mintz and Katz have provided data concerning the prevalence of diabetes mellitus among myocardial infarction cases both for their own series and from the literature[24, 74-78, 79] These prevalence data are reproduced below

	Males	*Females*
Wright Marple and Beck	7.1 % (Based upon 774 cases)	21.2% (Based upon 210 cases)

Doscher and Poindexter	5 1% (Based upon 354 cases)	18.9% (Based upon 80 cases)
Master Dack and Jaffe	6 7% (Based upon males among 350 cases)	26 0% (Based upon 150 cases)
Mintz and Katz	9 2% (Based upon 392 cases)	7 2 (Based upon 180 cases)
Total cases	18 0	650

The best prevalence from all these data is the weighted mean values for all the series which yields the values 7 1% of men with myocardial infarction are diabetics and 24 8% of women with myocardial infarction are diabetics The mean age of such infarction series is approximately 60 years

From the systematic community study at Oxford Massachusetts by Wilkerson and Krall[5] the prevalence rates of diabetes mellitus in a population sample at comparable mean ages were

For men at 60 years of age	5.2% of the population sample was diabetic
For women at 60 years of age	[illegible] of the population sample was diabetic

Suppose that the male diabetic at 60 years of age is more prone to develop myocardial infarction than the average male of 60 years of age in the population at large We may set the risk of the diabetic male at x times that of the non diabetic male For every case of myocardial infarction per 1000 non-diabetic men there would be x cases per 1000 diabetic men of the same age With this information the data above concerning the incidence of diabetes in 60 year old men in the population at large and the incidence of diabetes in the myocardial infarction series the value of x can be calculated The observed ratio of male non diabetic myocardial infarction cases to diabetic myocardial infarction cases is 92 9 to 7 1 In the population at large there would be 5 2 diabetic men for every 94 8 non-diabetic men Whatever the incidence rate of myocardial infarction is in non-diabetic men the rate for diabetic men has been set at x times that value Therefore the number of cases of myocardial infarction arising from the non-diabetic men is (94 8) times (the incidence rate) Out of the same 100 men the number of cases of myocardial infarction arising from the diabetic men is (5 2) times (the incidence rate) times (x) The ratio of non-diabetic infarction cases to diabetic infarction cases is therefore—

$$\frac{(94\ 8)\ \text{times (Incidence Rate)}}{(5\ 2)\ \text{times (Incidence Rate) times } (x)}$$

The (incidence rate) factor cancels out in this ratio leaving 94.8 over (5.2) times (x). But this must be set equal to the observed ratio of 92.9 over 7.1. Therefore

$$\frac{94.8}{5.2x} = \frac{92.9}{7.1}$$

Solving it is found that

$$x = \frac{(94.8)\ (7.1)}{(92.9)\ (5.2)} = \frac{673}{483} = 1.39$$

Therefore it turns out that even utilizing data which may be biassed toward overstating the hazard of coronary heart disease in diabetics the diabetic man at an average age of 60 years *is only 1.39 times as likely to develop coronary heart disease* as is the non diabetic man of the same age.

In an entirely analogous manner the risk of the diabetic women of 60 years compared with the non diabetic women is calculated. Here we have

$$\frac{75.2}{24.8} = \frac{92.8}{7.2x} \quad \text{or } x = \frac{(92.8)}{(75.2)}\frac{(24.8)}{(7.2)} = \frac{2301}{541} = 4.25$$

Therefore the diabetic woman at age 60 years has approximately *4.3 times the risk of coronary heart disease compared with the* non diabetic woman of the same age. It does appear even allowing for bias that there really is an appreciably excessive coronary heart disease risk in the 60 year old diabetic woman compared with the woman of the same age in the population at large.

IS DIABETES MELLITUS AN INDEPENDENT FACTOR IN DETERMINATION OF CORONARY HEART DISEASE RISK?

Diabetes mellitus is no exception to what must be our general approach to the evaluation of factors associated with coronary heart disease namely a determination of whether it operates as an *independent* or *new* factor or whether it operates through one of the two basic known factors the Atherogenic Index the diastolic blood pressure or both. Clinically and practically the answer to this question is of vast importance to the physician and to every person who has diabetes mellitus. For few issues are more crucial than to know whether *anything*

about diabetes per se is involved in acceleration of the development of sub-clinical coronary heart disease If not new vistas open both for the physician and the diabetic patient for whom he is the medical counselor

Evaluation of the extent to which diabetes mellitus may predispose to coronary heart disease through elevation either of Atherogenic Index or diastolic blood pressure or both requires some knowledge of the values of these variables in cross sections of *today's* diabetics Hypertension and overweight are known to be common findings in the older diabetic woman especially and there is good literature documentation of these findings The hypertension would itself be a predisposing factor and the over weight is known from independent studies to be associated with atherogenic index elevation However direct data in diabetic persons are still vital In the course of a large scale evaluation of lipoprotein levels as a predictive indicator for coronary heart disease (Table IV) the Donner Laboratory studied bloods from several thousand persons of the National Heart Institute evaluation of a cross section of the community of Framingham Massachusetts plus certain groups of industrial employees There were among these thousands of individuals a reasonable number of diabetic persons Of 31 diabetic females 24 were members of the Framingham Community study 7 were employees of the Eastman Kodak Corporation and 1 was an employee of the Los Angeles Civil Service Commission Of 69 diabetic males 32 were members of the Framingham Community study 20 were employees of the Eastman Kodak Corporation 11 were employees of the Los Angeles Civil Service Commission 5 were employees of United Air Lines Corporation and 1 was an employee of the Pan American Airlines Company Probably the overall group of diabetics is as reasonable a cross section of diabetics as could be obtained for study short of a mammoth effort It is certainly a better index of *the* diabetic population than a group chosen from a diabetic clinic or hospital The mean Atherogenic Index values and diastolic blood pressures for these diabetics are compared with those for their matched non-diabetic groups in Table XI IV The elevations in Atherogenic Index for diabetic males versus non diabetic males and for diabetic females versus non diabetic

females are appreciable and highly significant (p<<0.01). The blood pressure in diabetic males *is only slightly above that in the* non diabetic male and cannot be proven significant. The blood pressure in diabetic women is appreciably and significantly above that for the non diabetic women.

Risk accounting is performed in the manner described in Chapter V. For the diabetic man the Atherogenic Index of 97.0 units (Table XVI) corresponds to a coronary heart disease risk of 7.2 times that of the reference Atherogenic Index of 30 units. For the average non-diabetic man the Atherogenic Index of 81.7 units corresponds to a risk of 4.46. Therefore the incidence rate of coronary heart disease in diabetic men of this age is expected to be 7.2 over 4.46 equals 1.61 times that for the non diabetic man of the same age *based upon the Atherogenic Index* alone. The blood pressure difference of 2.0 mm between diabetic and non diabetic men was not provably significant. If it is real, then from Table XIV the relative risk for diabetic men versus non-diabetic men (for pressures of 87.0 mm and 85.0 mm respectively) is 5.30 over 4.98 equals 1.06. Therefore from diastolic blood pressure alone, the relative risk for diabetic men is between 1.00 and 1.06 that for non diabetic men of the same age.

TABLE XLIV

ATHEROGENIC INDEX VALUES AND DIASTOLIC BLOOD PRESSURES IN A CROSS SECTION OF DIABETIC PERSONS AND IN GROUP MATCHED NON DIABETIC PERSONS

MEN (69 diabetics)	*Mean Age*	*Mean Atherogenic Index (units)*	*Mean Diastolic Blood Pressure (mm Hg)*
Diabetics	52.8 years	97.0	87.0
Matched Non Diabetic Controls	52.8 years	81.7	85.0
Difference (Diabetics – Non Diabetics)		+ 15.3	+ 2.0
WOMEN (31 diabetics)			
Diabetics	51.5 years	98.3	93.6
Matched Non Diabetic Controls	54.3 years	78.2	87.4
Difference (Diabetics – Non Diabetics)		+ 20.1	+ 6.2

The overall or net risk is obtained by multiplication of that from Atherogenic Index by that from diastolic blood pressure (Chapter V) The overall coronary heart disease incidence rate for diabetic men is therefore predicted to be between 1 0x1 61 and 1 06x1 61 or between 1 61 and 1 71 times as high as that for the age matched non-diabetic man This is to be compared with the above described observed relative incidence rates (from myocardial infarction series) of 1 39 times in diabetic men as in non diabetic men for the same general age range This represents excellent agreement between the observed relative incidence rate and the rate predicted from the combination of Atherogenic Index and diastolic blood pressure Considering the nature of the material available for such a study the extent of agreement is close enough so that it can be stated that Atherogenic Index plus blood pressure effects account for the vast bulk if not all of the effect of diabetes mellitus in predisposing men to coronary heart disease

For the diabetic women the average Atherogenic Index of 98 3 units compared with 78 2 units for the age matched non diabetic women corresponds (Table XVI) to a relative risk of 7 43 over 3 84 or 1 93 times This accounts only for the con tribution to risk from the Atherogenic Index For the diabetic women the average diastolic blood pressure of 93 6 mm Hg com pared with 87 4 mm in age matched non-diabetic women corre sponds (Table XIV) to a relative risk of 6 44 over 5 37 or 1 20 times The overall or net risk obtained by multiplying that from Atherogenic Index by that from diastolic blood pressure is 1 93x1 20 = 2 31 This relative incidence rate is to be compared with that observed (myocardial infarction series) of 4 25 times Thus this approximate type of analysis indicates that the com bination of Atherogenic Index plus diastolic blood pressure accounts for the order of 54% of the overall increased risk for diabetic women compared with non diabetic women When con sideration is given to the sources of material and the relatively small series of diabetic women available it is entirely possible that essentially all the excessive risk of coronary heart disease in diabetic women is accounted for by the combined effects of

Atherogenic Index and diastolic pressure In any event it appears that these effects account for over half of the excessive risk

These *calculations indicate* that for diabetics as a group the diastolic pressure and the Atherogenic Index together account for the largest share of the excessive heart disease rate experienced If any other features of diabetes are *of any consequence* they can at best account only for a small part of the excessive risk There exists no valid scientific evidence in the literature to support the idea that some intrinsic feature of diabetes *per se* contributes in any way to an increased incidence rate of coronary heart disease among diabetics Indeed no previous study has ever been reported which attempted to ascertain quantitatively whether or not the diastolic blood pressure elevation and the Atherogenic Index elevation were a sufficient basis for the excessive heart disease risk of diabetics Speculations are rife concerning the possibility of metabolic and/or structural features surrounding capillary integrity in diabetics but no evidence whatever has come forth to show that such features are of any consequence what ever for the coronary arteries Reference to the capillary lesions of the retina and the kidney may be wholly irrelevant to the situation in the coronary arteries Indeed the observation of mas sive elevation of blood lipoproteins in diabetic retinopathy[76] and in diabetic nephropathy may even suggest that the hyperlipo proteinemia should be considered as a possible contributing pre cursor of those capillary lesions

The impression that diabetes *per se must* be a contributing factor to excessive risk of coronary heart disease over and above Atherogenic Index and blood pressure effects arises commonly from two erroneous sources First physicians are properly impressed that their diabetic patients do experience considerably more frequent coronary heart disease than their non diabetic patients *Often overlooked however is the fact that their* average diabetic patient *is older* than the average person in the population at large Diabetes is a disorder the incidence of which increases sharply with increasing age Thus even if considera tion is limited to adults in the 30 69 year age range it is readily demonstrable that the average age of men in the diabetic popula tion is *52 5* years compared with *46 3* years for non diabetic men

and 53 1 years for diabetic women compared with 44 1 years for non-diabetic women Since a 10 year difference in age would of itself lead to a tripling of the incidence rate of coronary heart disease the fact that diabetics in our population are 6 to 9 years older than non-diabetics would itself lead to an expected rate of coronary heart disease two to three times higher in the diabetics The way to avoid such erroneous impressions is always to compare groups on an age specific basis as was done in the earlier calculations of this discussion

The second erroneous source of the impression that diabetes *per se* must contribute to an excessive hazard of coronary heart disease is the expectation that diabetics would have to show the massive blood lipid elevations of the pre insulin period Such blood lipid elevation is *far* from necessary in order to explain excessive risk of coronary heart disease The data of Table XVI show what an increase in risk a rise of 10 Atherogenic Index units means Such rises are not massive at all and unless the nature of the risk tables is understood the wrong impression will be gained Indeed if many diabetics showed the massive blood lipid elevations expected in some quarters their hazard of coronary heart disease would be vastly above what it now is

PRACTICAL CLINICAL IMPLICATIONS OF THE NATURE OF THE ASSOCIATION OF DIABETES MELLITUS WITH CORONARY HEART DISEASE

Since it appears that Atherogenic Index elevation and blood pressure elevations are the prime contributors to the excessive hazard of coronary heart disease in diabetic patients (as in people in general) some important features of management of the diabetic patient need discussion These center around (1) the relationship of diabetic control to subsequent evolution of clinical coronary heart disease and (2) prognostic information for the diabetic patient

DOES STRICT CHEMICAL CONTROL OF DIABETES MELLITUS DECREASE THE HAZARD OF CORONARY HEART DISEASE?

Emotionalism much more than evidence has held the stage in this question of the value of strict chemical control of diabetes mellitus for prevention of premature vascular disease Some rational unbiased approaches have sorely been needed in this area *Ideally it should be possible to determine the age specific* incidence rate of a complication such as coronary heart disease by observing the fate of diabetics under various types of management regimens This it has been shown is easier to propose than to execute The questions of comparability of patient material from various clinics the many medical measures employed over and above diabetic control and a host of other features *have arisen to leave this problem largely unanswered*

It seems reasonable to state that since lipoprotein levels Atherogenic Index values and blood pressure together account quantitatively for most of the excessive hazard of coronary heart disease in diabetic patients one might profitably look at the relationship of chemical control with these variables The studies of diabetics in acidosis show a marked Atherogenic Index elevation *to characterize that state Therefore it is quite* apparent without further evidence that de control of diabetes *to this* extent is contra indicated as it is on other grounds as well But this is not the real clinical problem Rather it is the region of hyperglycemia and glycosuria *short of* acidosis that is of importance The advocates of strict chemical control would try to minimize hyperglycemia and glycosuria always mindful of course of the necessity of not overstepping into the highly undesirable region of hypoglycemic episodes Those who oppose strict chemical control have been unconvinced that hyperglycemia and glycosuria without acidosis are of much consequence and have therefore not been concerned about patients spending most of their time with moderate *hyperglycemia and some glycosuria*

Strisower and co workers [8] have recently presented direct evidence concerning the relationship of chemical control with serum lipoprotein levels and Atherogenic Index values *in this region short* of acidosis These studies were performed in a

group of 17 institutionalized diabetic schizophrenic women on the medical service of a large state hospital. The patients were all ambulatory. Since careful observation was possible for the group it was deemed feasible to raise or lower insulin dosage in such patients for periods of many weeks or months so as to achieve an alteration in mean fasting blood sugar levels. During such periods of "control" (high insulin dosage) and "decontrol" but without acidosis (low insulin dosage) serial lipoprotein analyses were made. There is no doubt that alteration in insulin dosage provoked alterations in chemical control for the chronic fasting blood sugar levels in essentially all patients were markedly lowered during high insulin dosage and raised during low insulin dosage. The overall findings of the Strisower study are presented in Table XLV. There is a highly significant appreciable average lowering of the Atherogenic Index associated

TABLE XLV

ALTERATIONS IN SERUM LIPOPROTEINS AND ATHEROGENIC INDEX VALUES IN RELATION TO CHEMICAL CONTROL OF DIABETES (17 PATIENTS)

Variable	Mean Level in Control Phase	Mean Level in Decontrol Phase	Difference Decontrol-Control
S$_f$8 1? Lipoproteins (mg/100ml)	385	41ɔ	+ 30 ($p < 0.001$)
S$_f$12 20 Lipoproteins (mg/100ml)	ı3	ı1	− 2 (Not significant)
S$_f$20 100 Lipoproteins (mg/100ml)	93	101	+ 8 ($p < 0.10$)
S$_f$100 400 Lipoproteins (mg/100 ml)	23	32	+ 9 ($p < 0.02$)
Atherogenic Index (units)	ı2	79	+ ı ($p < 0.01$)
Mean Fasting Blood Sugar (mg/100ml)	105	191	+ 86 ($p < 0.001$)
Mean Insulin Dosage (units)	49	13	− 36

Mean values of 150 blood samples representing a total study period of 279 patient weeks

Mean values of 178 blood samples representing a study period of 268 patient weeks. (Since some patients were in "decontrol" phases while others were in "control" phases, temporal variations in lipoprotein levels are not complicating factors in this study.)

with the lower blood sugars of the control (high insulin dosage) phase contrasted with the other phase These workers showed further that middle aged patients showed a larger effect than did very elderly diabetic patients Such data provide sound biochemical support for the concept that strict chemical control of diabetes is of value in reducing one major factor associated with increasing the risk of premature coronary heart disease It is hardly necessary to emphasize that this is *not* advocacy of insulin dosages sufficiently high as to provoke frequent episodes of hypoglycemia

PROGNOSIS FOR THE DIABETIC PATIENT

It is regrettable that the scientifically unsupported notion that *diabetes per se* implies a high risk of premature coronary heart disease should have gained wide credence The medical literature is replete with statements to the effect that although diabetics need no longer die of acidosis or coma they still are doomed to a complication of premature arteriosclerosis The *evidence* is quite otherwise In the discussion above it was shown in quantitative terms that the major share (if not all) of the excessive risk of a complication such as coronary heart disease arises from Atherogenic Index elevation or diastolic blood pressure or both But this is an *average* finding for diabetic patients A particular diabetic patient can have escaped both the lipoprotein Atherogenic Index elevation and the blood pressure elevation For this patient there is no reason for the physician to be gloomy with respect to the prognostic outlook nor to generalize the increased risk of diabetes to this patient If such a diabetic patient can maintain low or moderate Atherogenic Index and diastolic blood pressure values *his* risk of premature coronary heart disease may be expected to be many times lower than the risk for many persons who are not diabetic The point is that the physician has available to him valid measurable criteria that determine at a minimum the largest share of the risk of vascular complications namely the lipoprotein and blood pressure measurements Wide use of such criteria instead of the much less correct generalizations concerning diabetes will provide

exceedingly welcome relief to large number of diabetic patients who fear heart disease as an inevitable result of their being diabetic Furthermore utilization of these valid criteria of coronary heart disease risk can prove to be invaluable aids to the physician in management of the diabetic both in the areas of the planning of a regimen and in procurement of the patients maximum cooperation in the control of his disease

Chapter XIII

THE THYROID AND CORONARY HEART DISEASE

INTEREST has for decades centered about the question of the inter relationships of thyroid function blood lipid levels coronary arteriosclerosis and coronary heart disease The clinical literature on this subject is a maze of confusion contradictory statements and sweeping opinions based upon scanty evidence and in many cases no evidence whatever But few problems are of greater importance to the physician interested in coronary heart disease than to know the true status of the role of the thyroid and of thyroid hormone and its congeners There are several cogent reasons why this is true among which are

(1) Hypothyroidism spontaneous or iatrogenically induced elevates blood lipoprotein levels (especially S_f0 12 and S_f12 20) and hence elevates the Atherogenic Index

(2) Desiccated thyroid substance[79] thyroxine[80] and tri iodothyronine[81] have all been demonstrated to be potent for lowering blood lipoprotein levels and Atherogenic Index values not only in hypothyroid persons *but also* in euthyroid persons

(3) The classical mode of production of arteriosclerosis in animals ordinarily resistant involves the use of thyroid ablation either surgically by radiation or by thiouracil or related drugs

(4) *A vast clinical literature indicates that hypothyroidism* accelerates development of coronary arteriosclerosis

BASIC CONSIDERATIONS

The chief interest in this text is in the field of subclinical coronary heart disease that is the period when accumulation of

risk of future clinical coronary heart disease goes on silently undoubtedly via the mechanism of progressive narrowing of the coronary arteries It is therefore important to avoid confusing this phase of coronary heart disease with *extremis* phases of clinical coronary heart disease such as angina decubitus Thus preventive or therapeutic considerations that may apply to the person in the subclinical phase of coronary heart disease either before the first clinical episode or during the interim period between clinical episodes may not apply to the patient with severe angina pectoris or cardiac decompensation This differentiation is commonly missed in much of the medical literature on the subject of thyroid and coronary heart disease Let us suppose it has been demonstrated that administration of desiccated thyroid substance may intensify angina pectoris in some patients who already have angina pectoris This *need not necessarily* have any bearing whatever upon the question of utilization of desiccated thyroid substance (and related agents) for purposes of achieving and maintaining lowered lipoprotein levels and Atherogenic Index values in persons free of clinical manifestations of coronary heart disease

THE BLOOD LIPOPROTEINS AND ATHEROGENIC INDEX IN SPONTANEOUS MYXEDEMA AND INDUCED HYPOTHYROIDISM

The extremely high incidence of elevation in the blood cholesterol level both in spontaneous myxedema and in induced hypothyroidism have long been known to physicians In recent years with the availability of modern physico-chemical techniques it has been possible to identify the intimate nature of the blood lipid disturbance both in spontaneous and in induced hypothyroidism and myxedema The lipoprotein findings for untreated spontaneous myxedema are illustrated below for two typical cases

	S_f0 12 (mg/100ml)	S_f12 20 (mg/100ml)	S_f20 100 (mg/100ml)	S_f100-400 (mg/100ml)	Atherogenic Index (Units)
Case 1 44 year old woman	730	1 0	112	18	119
Case 2 60 year old woman	877	193	103	16	137

The major features of importance are the massive elevation in the S_f 0-12 and S_f 12-20 lipoproteins the absence of any appreciable elevation in S_f 20-100 and S_f 100-400 lipoproteins and the marked elevation of Atherogenic Index which results from the S_f 0-12 and S_f 12-20 lipoprotein elevation The induction of hypothyroidism and myxedema by surgical means by radio iodine or by pharmaceutical agents of the thiouracil type produces a hypercholesterolemia of the same form namely an elevation of S_f 0-12 and S_f 12-20 lipoprotein levels above the corresponding pre treatment levels *Therapy of myxedema with desiccated* thyroid substance thyroxine or tri iodothyronine results in a reduction in level of the S_f 0-12 and S_f 12-20 lipoproteins

The marked elevation of S_f 0-12 and S_f 12-20 lipoprotein levels and hence the Atherogenic Index in either spontaneous or induced myxedema would be expected to lead to an accelerated rate of development of subclinical coronary heart disease and therefore to a high risk of future clinical manifestations There exists no reason on a priori grounds to assume that Atherogenic Index elevation resulting from myxedema should behave any differently with respect to increasing coronary heart disease risk than would elevation for any other reason Physicochemically and chemically the lipoproteins of the S_f 0-12 and S_f 12-20 classes which become elevated in myxedema are similar to those which occur in health and in a variety of other diseases There is no reason why the risk tables of Chapter X should not be used in the case where lipoprotein elevation is produced by myxedema Yet there is current in some quarters the idea that the elevation in blood lipoproteins (or blood cholesterol) in *hypothyroidism or myxedema is safe, in that it neither* accelerates coronary arteriosclerosis development nor increases the risk of clinical coronary heart disease This idea is based upon inadequate evidence plus erroneous interpretation and analysis of what evidence does exist Blumgart and his co workers[8] have sponsored the view that the blood lipid elevation in hypothyrodism and myxedema does not accelerate coronary arteriosclerosis Their evidence for this view deserves careful appraisal These workers have had experience with the therapeutic use of induced hypothyroidism for alleviation of intractable angina pectoris and

congestive heart failure In a publication[53] dealing with eight patients who had survived one to thirteen years after surgical total thyroidectomy Blumgart and co workers drew the conclusion that The results demonstrate that progressive atherosclerosis of the coronary arteries is not a necessary concomitant of increased blood cholesterol levels in hypothyroidism or of the hypothyroid state This sweeping generalization would be important indeed if the evidence presented by Blumgart and associates could support it but the evidence does not do so The series of patients they reported included five men and three women

For the five men the following values are obtained from analysis of the data presented

Mean age at thyroidectomy	34 0 years
Mean initial blood cholesterol level	197 0 mg/100ml
Mean duration of life in the myxedematous state	8 3 years
Mean blood cholesterol during the period of life in the myxedematous state	335 2 mg/100ml

For the three women the following values are obtained

Mean age at thyroidectomy	40 3 years
Mean initial blood cholesterol level	193 0 mg/100ml
Mean duration of life in the myxedematous state	6 2 years
Mean blood cholesterol level during the period of life in the myxedematous state	277 3 mg/100ml

Based upon gross semi quantitative evaluation of the post mortem state of the coronary arteries the conclusion was drawn that the degree of involvement of the coronary arteries was certainly no greater and probably less than that generally witnessed in similar euthyroid individuals with the same disease process No evidence was presented for such similar euthyroid individuals to facilitate this comparison Among many questions that must be asked is Are these eight patients representative in their initial state before myxedema induction of euthyroid individuals The mean blood cholesterol initially for the five men was 197 0mg/100 ml From data in the literature[54] the mean cholesterol level (by similar methods) for men of this age in the population at large is 218 0 mg/100 ml The mean blood cho

The major features of importance are the massive elevation in the S_f0 12 and S_f12 20 lipoproteins the absence of any appreciable elevation in S_f20 100 and S_f100-400 lipoproteins and the marked elevation of Atherogenic Index which results from the S_f0 12 and S_f12 20 lipoprotein elevation The induction of hypothyroidism and myxedema by surgical means by radio iodine or by pharmaceutical agents of the thiouracil type produces a *hypercholesterolemia of the same form namely an ele*vation of S_f0 12 and S_f12 20 lipoprotein levels above the corresponding pre treatment levels Therapy of myxedema with desiccated thyroid substance thyroxine or tri iodothyronine results in a reduction in level of the S_f0 12 and S_f12 20 lipoproteins

The marked elevation of S_f0 12 and S_f12 20 lipoprotein levels and hence the Atherogenic Index in either spontaneous or induced myxedema would be expected to lead to an accelerated rate of development of subclinical coronary heart disease and therefore to a high risk of future clinical manifestations There exists no reason on a priori grounds to assume that Atherogenic Index elevation resulting from myxedema should behave any differently with respect to increasing coronary heart disease risk than would elevation for any other reason Physicochemically and chemically the lipoproteins of the S_f0 12 and S_f12 20 classes which become elevated in myxedema are similar to those which occur in health and in a variety of other diseases There is no reason why the risk tables of Chapter V should not be used in the case where lipoprotein elevation is produced by myxedema Yet there is current in some quarters the idea that the elevation in blood lipoproteins (or blood cholesterol) in hypothyroidism or myxedema is safe in that it neither accelerates coronary arteriosclerosis development nor increases the risk of clinical coronary heart disease This idea is based upon inadequate evidence plus erroneous interpretation and analysis of what evidence does exist Blumgart and his co workers[82] have sponsored the view that the blood lipid elevation in hypothyrodism and myxedema does not accelerate coronary arteriosclerosis Their evidence for this view deserves careful appraisal These workers have had experience with the therapeutic use of induced hypothyroidism for alleviation of intractable angina pectoris and

matous average men would have accumulated by the age of 42 3 years which is the age at which Blumgart s male patients died As a result of the myxedema induction and the elevation of Atherogenic Index of 45 units resulting therefrom those patients would have accumulated 45x8 3 or 374 units more than the average non myxedematous man Blumgart s males therefore at death would have accumulated a total of 2814 units (obtained by adding 374 to 2440) in comparison with 2440 units for non myxedematous men at this age Similar calculations are readily made for the women The average non myxedematous woman at 40 3 years has an Atherogenic Index of 55 5 units and by 46 5 years an Atherogenic Index of 59 5 units At 40 3 years such a woman would have accumulated 1790 units During the 6 2 years thereafter (corresponding to the myxedema period for Blumgart s female patients) average non myxedematous women would accumulate (6 2) (57 5) or 357 additional units giving a total accumulation of 1790 + 357 or 2147 units As a result of the myxedematous state Blumgart s three women would have accumulated an extra 25x6 2 or 155 units Therefore at 46 5 years which is the age of death of Blumgart s women they would have accumulated 2302 units in comparison with 2147 units expected for non myxedematous women of the same age

Elsewhere it has been shown that the total accumulation (measured by Atherogenic Index multiplied by time) parallels extremely closely the quantitative changes in degree of coronary arteriosclerosis with age in the United States wholly independent of any consideration of cause and effect relationships Therefore Blumgart could have expected his myxedematous men to have a 15 3% increase in degree of coronary arteriosclerosis compared with non myxedematous men of the same age corresponding to the 15 3% greater accumulation calculated above Similarly he could have expected a 7 2% increase in degree of coronary arteriosclerosis compared with non myxedematous women of the same age corresponding to the calculated 7 2% increase in accumulation due to the myxedema From the known extent of variation in degree of coronary arteriosclerosis in men of a particular age or in women of a particular age it can be estimated that to prove a 15 3% increase in degree of coro

lesterol level initially for the three women was 198 0 mg/100 ml For women of this age in the population at large the mean cholesterol level is 210 mg/100 ml If blood cholesterol level is related to coronary arteriosclerosis development it can be stated that the eight patients, *without* myxedema should have showed an average or slightly lower than average degree of coronary arteriosclerosis The crucial issue at hand is how much would the period of life these patients experienced with some elevation of blood cholesterol have increased the expected degree of coronary arteriosclerosis above average?

This question can be answered utilizing the concept of accumulation of coronary arteriosclerosis First since the blood cholesterol elevation in myxedema is almost wholly in S_f0 12 and S_f12 20 lipoproteins the extent of elevation of these lipoprotein classes can be calculated since they are known from chemical data to contain 34% cholesterol by weight Thus for the five men in the series the mean elevation of blood cholesterol of 138 2 mg/100 ml above the initial value corresponds to an elevation of S_f0 20 lipoproteins of 138 2 over 0 34 or 407 mg/100ml For the three women in the series the mean elevation of blood cholesterol of 79 3 mg/100 ml above the initial value corresponds to an elevation of S_f0 20 lipoproteins of 79 3 over 0 34 = 233 mg/100 ml Since these lipoproteins inculde the S_f12 20 which receives a weighting of 1 75 times that of the S_f0 12 lipoproteins the elevation in lipoproteins for the men corresponds to approximately a 45 unit increase in Atherogenic Index for the men and to a 25 unit increase in Atherogenic Index for the women On the accumulative basis where Atherogenic Index multiplied by time is considered (see Chapter VII) the average 34 year old man whose Atherogenic Index is 68 6 units will have accumulated 1834 units In the 8 3 year period (the length of time Blumgart s male patients were myxedematous this average man would accumulate additional units Since by 42 3 years his Atherogenic Index without myxedema induction would be 77 3 units the average Atherogenic Index for the 8 3 year period would have been 68 6 + 77 3 over 2 or 73 0 units Therefore the additional accumulation would have been 73 0×8 3, or 606 units Adding 606 to 1834 gives 2440 units which non myxede

to the pre therapy levels in spite of maintained administration of three grams of thyroid substance per day This apparent escape phenomenon has a reasonable explanation During the early period of administration of thyroid substance the patient has available the exogenously administered plus the endogenously produced thyroid hormone As administration of exogenous hormone continues endogenous thyroid hormone production is suppressed via the thyroid thyrotropin system until finally a point is reached where the *total* supply of thyroid available to the patient is not appreciably different from that available before the inception of administration of thyroid substance except that it is by such a time largely exogenous rather than endogenous in source A reasonable corollary of this explanation would be that in order to achieve maintained lipoprotein lowering by exogenous thyroid administration sufficient thyroid must be given so that even if complete shutdown of endogenous production of thyroid hormone occurs there would still be more thyroid available to the patient than was available before the administration of the exogenous supply From the long term studies of Strisower and co workers[8] it appears that with doses of 4 or 5 grains of U S P desiccated thyroid substance per day such a point is reached for most persons within the usual ranges of lipoprotein distribution With these doses the level of lipoproteins is lowered and is maintained lower without any evidence of an escape phenomenon The magnitude of lowering of lipoprotein levels that were achieved with doses of 5 grains of desiccated thyroid substance per day is shown in the data of Table XLVI There the 59 cases studied extensively by Strisower have been segregated into three separate groups ranked according to initial level of the various lipoprotein classes Thus not only is the effect of thyroid substance demonstrable but its relationship with the initial lipoprotein status of the subject can be ascertained Inspection of these data shows that with a dose of 5 grains of thyroid substance per day there occurs a sustained lowering in mean level of all four lipoprotein classes S_f0 12 S_f12 20 S_f20 100 and S_f100-400 over the entire 36 week period of hormone administration For any one of the four lipoprotein classes the extent of reduction in lipoprotein level as a result of thyroid administration is greatest

nary arteriosclerosis among such male myxedema patients com pared with non myxedematous men would require careful quantitative assessment of degree of sclerosis in a series of about 100 myxedematous men and 100 non myxedematous men of the same age The demonstration of a 7 2% increase in coronary arteriosclerosis for the myxedematous women would require care ful quantitative study of about 300 myxedematous women s cor onary arteries and those of about 300 non myxedematous women of the same age Yet by semi quantitative grading Blumgart and his associates have made the decisions on five male patients and three female patients respectively without even presenting any data for matched non myxedematous patients The only conclu sion reasonable in the light of these considerations is that the material studied by Blumgart and associates was entirely inade quate and hence unsuitable for attempting any answer to the *question of the relationship of myxedema hypercholesterolemia* and arteriosclerosis Certainly their evidence should in no way even suggest the idea that the blood lipoprotein and Atherogenic Index elevation in patients with myxedema are of different mean *ing for coronary disease than they are in any other persons*

THE EFFECT OF DESICCATED THYROID SUBSTANCE *UPON SERUM LIPOPROTEIN LEVELS AND* ATHEROGENIC INDEX VALUES

Strisower and co workers [9] have carried out extensive investi gations of the effect of desiccated thyroid substance upon the various lipoprotein classes *Dosage* of thyroid substance is a highly critical factor in such studies for depending upon dosage and time of blood sampling *apparently* paradoxical results may be obtained With a dose of one to two grains of desiccated thyroid substance daily in most euthyroid adults very little altera tion in lipoprotein level is observed With a dose of three grains per day from the start most euthyroid subjects experience an appreciable lowering of S_f0 12 and S_f12 20 lipoprotein levels during the first few weeks of administration of the thyroid Thereafter there occurs in most cases a progressive rise in the levels of these lipoproteins completely or almost completely back

effect of administration of 5 grains per day of thyroid substance on the Atherogenic Index values for the 39 patients described above is presented in Table XLVII The patients are ranked in that tabulation upon their initial pre thyroid Atherogenic Index values It is evident that the group with very high Atherogenic Index values showed a very marked drop in Atherogenic Index value in response to continuous administration of desiccated thyroid substance This is of course precisely the group that would clinically be considered to be in need of lowering of the Atherogenic Index value with respect to prophylaxis of future coronary heart disease

In the discussion of familial factors in coronary heart disease (Chapter VI) the families characterized by massive elevation of S_f0 12 or S_f0 12 and S_f12 20 lipoprotein levels were described These families show the same type of lipoprotein derangement which characterizes myxedema although they show no clinical stigmata of myxedema Such families *none too* rare in the United States population are known to have an inordinately high risk of clinical coronary heart disease for those members of the family who *do* inherit the lipoprotein abnormality Both from the biochemical viewpoint and for possible practical prophylactic reasons the response of persons characterized by this particular

TABLE XLVII

EFFECT OF FIVE GRAINS OF DESICCATED THYROID SUBSTANCE PER DAY UPON ATHEROGENIC INDEX VALUES IN RELATION TO PRE THERAPY ATHEROGENIC INDEX VALUES

Mean Initial Atherogenic Index (units)	*Mean Atherogenic Index After 36 weeks on 5 Grains of Desiccated Thyroid Daily (units)*	*Change in Mean Atherogenic Index (units)*
Overall Group of 39 Cases		
0 0	52 0	− 18 0
The 10 Cases with highest Initial A.I Values		
94 1	64.0	− 30 1
The 19 Cases with intermediate A.I Values		
71 5	53 1	− 18 4
The 10 Cases with lowest Initial A.I Values		
43 0	37 1	− 5.9

TABLE XLVI

BLOOD LIPOPROTEIN RESPONSE TO DAILY ADMINISTRATION OF FIVE GRAINS OF DESICCATED U.S.P. THYROID SUBSTANCE IN RELATION TO PRE-THERAPY LIPOPROTEIN LEVELS

Range of Levels (mg/100ml)	*Mean Initial Lipoprotein Level*	*Number of Subjects*	*Lipoprotein Level after 36 weeks on 5 grains of thyroid daily (mg/100ml)*	*Change in Mean Lipoprotein Level (mg/100ml)*
S_f0-12 Lipoproteins				
Over 400	127	16	340	− 87
300-400	350	15	295	− 55
Below 300	218	8	184	− 34
S_f12-20 Lipoproteins				
Over 100	145	8	47	− 98
50-100	76	17	29	− 47
Below 50	37	14	23	− 14
S_f20-100 Lipoproteins				
Over 100	120	13	94	− 26
70-100	81	10	73	− 8
Below 70	54	16	54	0
S_f100-400 Lipoproteins				
Over 50	88	10	45	− 43
25-50	36	10	21	− 15
Below 25	16	19	13	− 3

in those individuals initially characterized by the highest levels of that particular lipoprotein class, is somewhat less for the initially intermediate group, and is least for the group with the lowest lipoprotein levels. One possible interpretation of these findings is that individuals with the highest lipoprotein levels may be *relatively* deficient in thyroid hormone availability even though on usual clinical grounds no evidence of frank hypothyroidism is present.

PRACTICAL CLINICAL IMPLICATIONS OF THE EFFECT OF EXOGENOUS THYROID SUBSTANCE UPON SERUM LIPOPROTEIN LEVELS

With respect to the potential application of the profound effect of desiccated thyroid subtance upon blood lipoproteins, it is of great interest to know how the overall Atherogenic Index value is affected by the administration of thyroid substance. The

TABLE XLVIII

Results of ... $S_{p}B$ ... Reported ... to Desiccated Thyroid Substance

Case No.	Age & Sex	$S_{p}B$ 12	$S_{p}I$	$S_{p}B$ 100	$S_{p}I$ 100–400		Maximum Daily Dosage and Duration	(per d)	(per d)	$S_{p}B$ 1	$S_{p}I$ 2	$S_{p}B$ 100	$S_{p}I$ 100–400		Time
1	18M	130	1	80	19	3 gr for 11	19	108	180	19	1,0	(	109	11 months
	F 6 8	131	8	0	9	gr for	10	111	11	10	14	1	73	19 months
3	M 13	1	43		81	5 grs for 3 mo	10	41	1 5	3	31	(	8	1 months
4	30F CC	98	13		9	gr for 10	133	136	18	9	C2	1	9	12 months
	10F 533	61	16	8	73	grs for 9 mo	1 C	1 9	3C	3C	77	19	(	11 months
C	11F 8	131	C1	0	11	grs for 4 mo	71	98	1C1	1	93	31	81	21 months
7	33F 038	118	83	C	130	gr for 1 10	11	114	1 9	CC	82	35	9	21 months
8	81 C17	79	31	8	8C	grs for 5 mo	81	8C	99	41	31	9		11 months
9	10M 9 0	01	110	10	148	7 gr for 9 mo	180	1	CC)	13	139	50	193	11 months
10	11F 93	1	98	–	148	8 grs for 4 mo	131	147	88	98	112	23	100	11 months
11	1 81	110	7	10	11	3 gr for	1	9	08	13	22	1	C3	21 months
12	19M 10	107	133	0	161	1 grs for 3	1 0	1C9	90	108	1,9	31	11	1 months
13	8F 889	1	218	19	117	1 gr for 11	1 1	1 1	91	11	1C1	0	119	7 months
14	3M 8 C	117	151	C	143	2 gr for 2 mo	1 6	1 9	C C	11	291	11	1C8	C months
1	18F 1033	110	1C1	31	1C	4 grs for [illegible]	1CC	1C1	01	133	1 3	0	19	months
1C	19M 550	111	116	28	113	3 grs for 1 mo	189	177	431	103	19	90	89	13 months

These studies are still in progress. The maximum thyroid dosage is simply that which has been reached at the time of this evaluation and in no way implies maximum thyroid tolerance of the patient.

In general the patients were started with a dosage of 1 grain of desiccated thyroid per day and the dose built up over varying periods thereafter depending upon the patient.

familial hyperlipoproteinemia is of intense interest Sixteen such subjects have been treated with desiccated thyroid substance for varying periods of time The results achieved are presented in Table XLVIII It is evident that such persons are distinctly capable of responding to administration of thyroid substance with a marked lowering in the level of S_f0 12 and S_f12 20 lipoprotein Furthermore many such responses occur without weight loss or even in the face of a net gain in weight Clinical evidence of thyroid toxicity has been a rare occurrence in these subjects

The clinician reflecting upon these large effects of exogenous thyroid substance on serum lipoprotein levels and Atherogenic Index values will in many instances, still be hesitant to consider the use of exogenous thyroid substance as a preventive measure in the sub clinical phase of coronary heart disease He will undoubtedly be mindful of the fact that caution is indicated in the rate of buildup of the dosage of thyroid substance in patients with myxedema where too energetic thyroid replacement therapy has been reported to result in myocardial infarction The presumed mechanism in such cases is an increased caloric expenditure by the myocardium in the presence of an embarrassed coronary blood flow resulting from extensive coronary arteriosclerosis The clinician will also be mindful of the reports that angina pectoris can be exacerbated by the administration of thyroid active agents and that intractable angina pectoris can be relieved in some cases by thyroid ablation But the patient with frank and long standing myxedema and the patient with intractable angina pectoris are hardly those upon whom the broad interest in possible use of thyroid substance to diminish the rate of progression of sub-clinical coronary heart disease is focussed Rather the persons of interest are relatively youthful individuals with massive elevation in lipoprotein levels and Atherogenic Index values The outlook for such persons is gloomy unless their lipoprotein status can be improved and maintained so for long periods of time Some such subjects will show minor calorigenic effects of exogenous thyroid substance others will not Careful clinical observation of these persons during administration of thyroid substance is essential Biochemistry biophysics and mathematics can aid

Chapter XIV

OCCUPATION, STRESS, PHYSICAL EXERCISE, AND CORONARY HEART DISEASE

It is not the need of a chapter in this book in which to place residual material that leads to the grouping of occupation stress and physical exercise together in the discussion of each in relationship with coronary heart disease Rather this grouping results from the observations (to be detailed below) showing that occupation is in some way related to coronary heart disease and from the emphasis placed by some investigators either upon stress or physical exercise as the factors accounting for the occupational differences in incidence rate of coronary heart disease Unfortunately this area is considerably beclouded by semantic difficulties by emotionalism by pre-conceived concepts and by inadequate quantitative data Yet it is an important area for every physician faces daily questions referable to this area from his patients with coronary heart disease and from those who would like to avoid that disease

Semantic and measurement difficulties surround one of these factors especially namely stress Definitions of emotional occupational and life stresses are nearly as frequent as are investigators of the problem Qualitative impressions are rife Many are certain that the *pace of modern living* create stresses upon man never before equalled in history although even semi-quantitative evidence to support this statement has not yet been forthcoming Such workers point to the apparently real rising incidence of clinical coronary heart disease in Western countries over the past several decades and to the pace of living in these regions over the same time period Then they state flatly that it is obvious that the stress is clearly the basis for the increase in

clinical medicine, but they are hardly intended to be a replacement for seasoned clinical judgment If calorigenic effects should develop and should be deemed clinically dangerous then these particular persons probably cannot take advantage of the lipoprotein lowering effect of thyroid substance Most persons receiving thyroid substance will not show calorigenic effects sufficient to warrant discontinuation of thyroid administration

There have recently been reported a few cases receiving tetraiodothyroacetic acid[86] where lowering of blood lipids was achieved without appreciable alteration of the basal metabolic rate or other evidence of calorigenic effects This has raised hopes[9] that a pharmaceutical agent might be at hand which might provide the desirable effect upon blood lipoprotein levels while averting the unwanted possible calorigenic action However *these studies were not controlled by comparison* of the effects of desiccated thyroid substance on the same patients a highly necessary control Strisower and co workers showed that many patients in their series exhibited no evidence of appreciable calorigenic action such as weight loss or such effects as pulse rate increase, but still showed marked lowering of lipoprotein levels Nevertheless inasmuch as the remarkable effect of thyroid active substances upon blood lipoproteins has not been proved to be part of the calorigenic action of such agents pharmacologic studies directed toward achievement of derivatives which may dissociate these effects appear worthwhile

lying evidence may perhaps be somewhat stronger than critical evaluation would reveal it to be

OCCUPATION AND CORONARY HEART DISEASE

Consideration of this overall area may logically start with evaluations of occupation in relation to coronary heart disease for occupational stresses have been indicted by many as a major predisposing factor in coronary heart disease There do exist some factual data concerning the incidence rate of coronary heart disease in various occupational categories Morris[99] has been especially active in the evaluation and presentation of data pertinent to occupational incidence rate of clinical coronary heart disease His studies indicating a higher frequency of clinical coronary heart disease and a more severe form of coronary heart disease in the drivers of double-decker London buses compared with the conductors of such buses are now classic in the medical literature He has further provided data summarizing the incidence rate of clinical coronary heart disease in a wide variety of occupational categories for Great Britain These occupational groups and their coronary heart disease incidence rates are listed in Table XLIX There is every reason to consider that occupational differences of appreciable magnitude *do* exist in the incidence rate of clinical coronary heart disease well above any attributable to statistical sampling errors It is rather the step beyond this conclusion which is so difficult *Why do* occupational differences in incidence rate of clinical coronary heart disease exist Morris recognized the difficulties involved in interpretation of the occupational differences in coronary heart disease and especially that no one ready explanation would be considered to explain all the observations Among the major possibilities that have received consideration are (1) The type of person who in general makes the *choice* of a *particular occupation* or has it effectively made for him by circumstances may differ in many ways from the type of person in some other occupation Physical habitus muscularity intellect temperament background and a host of other factors could well help determine who is to be found in a particular occupation Should this be the major basis

incidence rate of clinical coronary heart disease Yet no such conclusion seems obvious to the critical observer who places some reliance upon quantitative methods in modern medical science It has been pointed out previously (Chapter XIII) that the quantitative disciplines do not in any way invalidate the continuing necessity for clinical judgment in medicine but on the other hand this statement does not imply that unbridled impression can serve as evidence in lieu of quantitative measurement

The essence of the difficulty with the evaluation of stress as a potential factor in coronary heart disease lies in the variability of its definition and the almost complete absence of satisfactory methods for its measurement even on a crude semiquantitative basis This necessarily makes any reasonable evaluation of its possible significance difficult at a minimum One finds it unsatisfactory to accept quantitation in terms of stressful situations personal social economic or other inasmuch as what really is of concern is the effect of any particular stressful situation upon a particular individual A set of circumstances mildly stressful to one person can readily be conceived to be either mildly moderately or overwhelmingly stressful to some other person Hence what is needed is some method of quantitating the nature of the interaction of the situation with the individual and the extent of effect of such interaction upon that individual Even if such a method were of semi-quantitative character but objectively executed involving a grading of stress on a scale of plus one to plus four enormous progress could then be made in the evaluation of any possible relationship of stress in humans with the evolution of coronary heart disease But no such method has been described and worse yet most evaluations to date have involved retrospective evaluation of the stress once the biochemical or clinical alterations of interest had already been observed a procedure fraught with massive danger of bias Nevertheless it is of some merit to examine what evidence has been brought forward purporting to relate stress to coronary heart disease in man Especially is this important to do since some of the advocates of the stress concept are rather positive in their assertions leaving the impression that the under

require identification and a determination of whether or not *new* or *independent* information is provided with respect to coronary heart disease This point deserves amplification Suppose that the circumstances of a particular occupation were such as to modify significantly the dietary habits of persons in that occupation either as a result of location availability of certain foods or social circumstances within the occupation It would be possible that animal sources of fat for example might be increased in the habitual diet From previous considerations (Chapter X) it would be predicted that this dietary alteration would provoke an elevation of the S_f0 12 and S_f12 20 lipoproteins and through this the Atherogenic Index would be elevated and would hence lead to an increase in expected incidence rate of coronary heart disease for the occupational category itself But this would really not be new or independent information concerning factors involved in the evolution of coronary heart disease for it would have reduced itself to one of the two known basic factors namely blood lipoproteins and blood pressure level To be sure it would be important to identify the fact of a habitual alteration in diet being a basis for an occupational predisposition to coronary disease but this would be a discovery of minor magnitude in comparison with adding an additional basic factor to the two which are known

(2) The many and varied stressful features of certain occupations have been considered by Morris and others as a possible basis for observed differences in coronary disease incidence rates Morris concluded that considering all the occupational groups involved it would be difficult to frame a hypothesis built around stress of the occupation that would be satisfactory to explain the findings Others have quickly pointed to the differences between the stressful factors in the occupational life of a bus driver in congested London traffic in comparison with the presumed lesser stresses in that of the conductor of the double-decker bus Whether the bus driving in congested traffic is stressful or relaxing to a London bus driver is not as simply decided as some would make it seem Much depends upon the reaction of the type of man who is a bus driver in the evaluation of what stress he experiences in his occupation Even if it were conceded that bus

TABLE XLIX

DEATH RATE FROM CORONARY HEART DISEASE IN RELATION TO OCCUPATION
(45 64 YEAR OLD MEN

ENGLAND AFTER MORRIS)

Occupational Category	*Death Rate from Coronary Heart Disease (number per million per year)*
Hairdressers etc	880
Makers of Textile Goods	770
Typists and other Clerks (Non Civil Service)	730
Fitters Mechanics Tool Makers etc	560
Messengers and Porters etc	500
Railway Engine Drivers	480
Postmen and Sorters	460
Boot and Shoe Makers Repairers	450
Smiths and Skilled Forge Makers	420
Metal Machinists	380
Coal Hewers and Getters	290
Water Transport Dock Laborers	270
Coal Mine Workers below ground except Hewers and Getters	230
Other Workers in Building etc	170
Agricultural Gardeners Laborers etc	150

for the differences in occupational incidence of coronary heart disease the problem would reduce itself to that of understanding what features of particular types of persons account for an inordinate susceptibility to coronary heart disease Illustratively if obese men should represent a much higher proportion of those engaged in one occupation versus others that occupation would be expected to show a higher incidence rate of coronary heart disease than the others because obesity is definitely known to increase the risk of such disease (See Chapter IX) This would be true even if no features of the occupation or the interaction of the individual with his occupational environment existed On the other hand it could be that persons of a particular type might tend to select a certain occupation and that the interaction of the occupational environment with that particular type of individual might lay the groundwork for future manifest coronary heart disease In such an event that interaction would

and blood pressure or whether it provides a third factor of *independent* importance in coronary heart disease. Occupational studies, including the physical activity factor, are unquestionably needed to provide some of the critical answers.

RELATIONSHIP OF OCCUPATION WITH FACTORS KNOWN TO BE OF IMPORTANCE IN CORONARY HEART DISEASE

(a) Blood Lipoproteins, Atherogenic Index and Occupation

Several years ago the author and his colleagues undertook some long-range studies of the various characteristics of the human population which influence habitual distribution of blood lipoproteins. With the already available knowledge that even for a specific age and sex group considerable variability still characterizes the population with respect to blood level of such lipoproteins as the S_f 0-12, S_f 12-20, S_f 20-100 and S_f 100-400 classes, it seemed extremely worthwhile to make a continuing effort to ferret out possible bases for such variability. Further serial study of population groups allows for the possibility of understanding some of the sources of variability of lipoprotein level within individual subjects. Occupational category was considered as one major variable of importance for study. Since it was desirable to eliminate certain types of extraneous sources of possible variation, the decision was made to study subjects in one industry working and residing in one general locale. In this way such possible sources of variation as climatic, geographic, and general features of the occupational environment are greatly minimized. Of course, the persons who work in one industry do have a previous background of differing geographic contacts, of having been in other industrial locations, and other features that render them heterogeneous. Nevertheless the common environment they share at the time of study, which for most of them was over one year after they had been employed in this single industrial area, would have tended to decrease heterogeneity in as practical a way as is possible for such studies. In this industry* a reasonable distribu

* University of California Radiation Laboratory at Livermore, California. (Employees number approximately [illegible]00.)

driving were more stressful than conducting there remain numerous other pairs of occupations differing in coronary disease incidence rates where such possible stress differences are not so apparent For example clerks in England have a higher coronary heart disease rate than postmen Assessment of stress factors for these two groups is not immediately obvious Unfortunately many who have assigned stress ratings to occupational groups have done so *retrospectively* once it was known which occupational group had the higher incidence rate of coronary heart disease It is regrettable that no more objective and quantitative approach to stress evaluation is available to replace the highly subjective retrospective one

(3) *Physical Activity in Occupations* Morris felt that his own evidence as a whole pointed most strongly to physical activity of the occupation as the feature of prime importance in determination of the incidence of coronary heart disease for the occupation Thus the bus drivers in London double deckers *seated* in their occupational activity for some eight hours of every working day do have far less activity *at work* than the conductors who make numerous trips up and down the bus stairs daily Upon review of the other occupational categories Morris found a reasonable inverse relationship between the physical activity of the occupation and the incidence rate of clinical coronary heart disease This inverse relationship appears from Morris data to be well established The important question which follows is How does it operate? Does physical activity at work of and by itself really provide some degree of protection against coronary heart disease? If it does would advocacy of physical exercise for those in more sedentary occupations be indicated in the effort to minimize their risk of coronary heart disease? These are points of enormous practical clinical consequence Clearly it would be essential to learn whether the physical activity *per se* of certain occupations is the essential feature or whether this is a reflection of some other feature known or unknown If physical activity is important it must operate by some definable mechanism In approaching this issue of mechanism it would be important to determine whether physical exercise (if it be a factor) in any way influences the two major known factors blood lipoproteins

and blood pressure or whether it provides a third factor of *independent* importance in coronary heart disease Occupational studies including the physical activity factor are unquestionably needed to provide some of the critical answers

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* University of California Radiation Laboratory at Livermore California (Employees number approximately [illegible] 00)

tion of occupations is represented, including unskilled labor highly skilled labor, clerical professional scientific and executive groups

In all twenty nine occupational listings obtained from the personnel department records characterized the individuals from this population sample under study All subjects had periodic complete medical examinations at intervals of eighteen months, at which time the lipoprotein analyses were made It is understood that at times a particular personnel listing e g engineer can mean work loads differing appreciably within the category from individual to individual Thus the physical activity at work for each engineer can hardly be expected to be identical but it was not deemed feasible to sub-categorize so extensively as to arrive at a great multiplicity of sub groups each containing so few individuals as to make analysis of the findings impossible Therefore each of the twenty nine occupational groups was kept together as a single entity The age for each group was not identical ranging plus or minus approximately five years on either side of 35 0 years of age For comparison of lipoprotein levels in one occupational category with another the small correction of the lipoprotein level for each category to what it would be at 35 0 years was made Such small corrections are extremely good since the age trend for each lipoprotein class is very well established (Table XXIV) The data for all twenty nine occupational categories are presented in Table L The range of mean Atherogenic Index values for the various occupational categories is truly startling Excluding some of the categories where limited numbers of subjects were available for study some of the differences observed are obviously real and of major magnitude For example the series of fifty custodians show the low mean Atherogenic Index of 60 6 units which may be compared with the over all group of *all* occupations for which the mean Atherogenic Index is 69 1 units The difference of 8 5 Atherogenic Index units is so large that sampling errors alone would lead to this large a difference about once in one hundred times (See Table L for method of proving this In this case SE = 3 5 t = 2 4) Similarly comparison of one of the categories showing a very high value e g tool and die makers with a mean Atherogenic Index

TABLE 1

Atherogenic Index Values in Twenty Nine Occupational Categories in One Industry (Male Subjects)

(Ranked from Highest Atherogenic Index Values to Lowest)

Occupational Category	Number of Men	Mean Age (years)	Atherogenic Index (adjusted to 35 0 years) (units)
Computer and Duplicating Machine Operators	[illegible]	31 1	[illegible]9 6
Truck and Bus Drivers	24	33.6	[illegible]9 4
Buyers	11	39 0	77 8
Tool and Die Makers	6[illegible]	36 0	[illegible] 7
Mathematicians	61	28.3	75 9
Laboratory Technicians	47	31.[illegible]	[illegible] 8
Journeyman Machinists	7	36 9	75.6
Firemen	19	36.5	7[illegible].3
Painters	[illegible]	41.2	72.2
Mechanical Technicians	90	34 8	71 [illegible]
Carpenters	21	3[illegible] 4	71 4
Welders	14	39 4	[illegible]0.6
Riggers and Equipment Movers	10	36.3	69 7
Electricians	43	3[illegible] 7	69 7
Engineers	2 6	3[illegible] 4	69 6
Physicists	2[illegible]7	30 6	69 4
Draftsmen	110	33 1	69 [illegible]
Executives (Assistant and Junior Classifications)	68	[illegible] 3	68 6
Steam Fitters and Boiler Operators	[illegible]	43.2	68.3
Clerks	[illegible]3	32 3	67.8
Electronic Technicians	1 0	3[illegible].6	67 8
Chemists		31.[illegible]	6[illegible].6
Machinist and Machinists Helpers	4	37 4	6[illegible] 7
Police Officers	10[illegible]	41 4	6[illegible] 9
Accelerator Operators	0	31 4	63 1
Storekeepers	30	3[illegible].2	6[illegible].8
Laborers	40	39 9	61 4
Custodians	0	49 1	60 6
Sheet Metal Worker	22	43 [illegible]	[illegible].2
Overall Group (All Occupations)	1883		[illegible]9 1

Standard Deviation of the Atherogenic Index for the overall group is approximately units Therefore to test whether the mean for any occupational group is significantly different the t test can be applied The standard error is $SE = \frac{2[illegible]}{\sqrt{n-1}}$ wherein is the number of subjects in the group If the difference between the Atherogenic Index for any single category and the overall group divided by S E. is over .5 (the t value) then there is less than one chance in 100 that the difference is not real

value of 77 7 units with a category with a low mean Atherogenic Index value e g custodians with a mean Atherogenic Index value of 60 6 units reveals that there is less than one chance in 1000 that so large a difference could arise by sampling alone The conclusion is safe that the difference observed is real

It is of major consequence that real and *large* differences in mean Atherogenic Index values exist between men in various occupational categories An estimate of the meaning of some of the differences observed is readily made by reference to Table XV Thus, since differences such as those between values of 75 and 60 Athrogenic Index units have been shown to exist incidence rates of coronary heart disease can be expected to differ by a factor of 4 97 over 2 59 or 1 9 *times* on the basis of the Atherogenic Index alone! Therefore some insight is available as to part at least of the basis for occupational differences in incidence rate of coronary heart disease What is of importance to determine is *why* some occupational categories should show different Atherogenic Index values from others Such features as the type of person who enters the occupation the relative weights of the individuals their smoking habits, and their dietary habits deserve evaluation since such features have been shown to be of consequence with respect to Atherogenic Index values The relative weights and the cigarette smoking habits for the men in the various occupational categories of Table L are available since their weights were measured and they had been questioned concerning cigarette smoking during the examination These data are presented in Table LI for each of the occupational categories Also in this table the combined mean value for all occupations characterized by Atherogenic Index values above the overall mean and the combined mean value for all occupations with Atherogenic Index values below the overall mean is presented Neither for relative weight nor for cigarette smoking can it be demonstrated that those occupations with high Atherogenic Index values are different from those occupations with low Atherogenic Index values Therefore it is clear that the broad features of the difference in Atherogenic Index with occupational categories cannot be explained either from differences in weight of the individuals or from differences in cigarette smoking habit

TABLE LI

RELATIVE WEIGHTS AND CIGARETTE SMOKING HABITS IN OCCUPATIONAL CATEGORIES RANKED UPON ATHEROGENIC INDEX

Occupational Category	*Number of Men*	*Mean Atherogenic Index (units)*	*Mean Relative Weight*	*Mean Number of Cigarettes Smoked Per Day*
Computer and Duplicating Machine Operators	[illegible]1	9 6	1 08	10
Truck and Bus Drivers	[illegible]4	9 4	1 06	8[illegible]
Buyers	11	[illegible].8	1 13	1 [illegible]
Tool and Die Makers	6[illegible]	77 7	1 0[illegible]	11 [illegible]
Mathematicians	61	73 9	0 [illegible]	8 0
Laboratory Technicians	4[illegible]	73 8	1 0[illegible]	11 4
Journeymen Machinists	7	[illegible]3 6	1.0[illegible]	9[illegible]
Firemen	19	[illegible] 3	1 16	[illegible]0 1
Painters	1[illegible]	7[illegible].2	1 02	1[illegible] 1
Mechanical Technicians	90	71 7	1 0[illegible]	12 1
Carpenters	[illegible]1	71 4	1 06	10 9
Welders	14	[illegible]0 6	1.06	8.3
Riggers and Equipment Movers	10	69 7	1 07	10 5
Electricians	43	69 7	1 06	13.3
Engineers	2[illegible]6	69.6	1 0[illegible]	8 9
Physicists	2[illegible]	69 4	1 02	[illegible]
Draftsmen	110	69.2	1 02	9 4
Executives (Assistant and Junior Classifications)	63	68 6	1 0[illegible]	15 9
Steamfitters and Boiler Operators	[illegible]1	68 5	1.0[illegible]	[illegible] 9
Clerks	[illegible]3	67 8	1.00	13 4
Electronic Technicians	170	6[illegible] 8	1 03	9 8
Chemists	[illegible]7	67.6	1 0[illegible]	7 1
Machinists	4	66 7	1 03	10.[illegible]
Police Officers	10[illegible]	6[illegible] 9	1 03	1[illegible] 3
Accelerator Operators	70	63 1	1 01	8 9
Storekeeper	30	6[illegible].8	1 02	10 1
Laborers	40	61 4	1 07	[illegible] 0
Custodians	0	60 6	1 03	9 0
Sheet Metal Workers	2[illegible]	5[illegible].2	1 04	1[illegible]
All Occupations with Atherogenic Index Means Above 69 1 (the overall mean)	1133	[illegible]4	1.041	9 4
All Occupations with Atherogenic Index Means Below 69 1 (the overall mean)	[illegible]0	6[illegible]	1 015	10 9

The failure of difference in body weight to explain the Atherogenic Index difference with occupation does not rule out the possibility that fitness may be important in this connection The relative weight determination does not of course distin

guish body weight made up of fat from that made of muscle for example It would still be possible that whereas the occupations characterized by low Atherogenic Index values do not show lower body weights they might still represent individuals with less body fat and more muscle than the occupations with high Atherogenic Index values This brings us to the question of the physical activity associated with various occupations Four of the occupations with the lowest mean Atherogenic Index values the laborers the custodians the accelerator operators and the store keepers are all characterized by extensive physical activity at work The four occupations with the highest mean Atherogenic Index values the computer and duplicating machine operators the truck and bus drivers the buyers and the tool and die makers are certainly characterized by much less physical activity at work It is not as readily apparent however that the occupations with an intermediate mean Atherogenic Index value are characterized by an intermediate degree of physical activity at work However other factors may in part operate here too For example the physicists do smoke significantly fewer cigarettes than the group as a whole which will to some extent alter their position on the Atherogenic Index scale Also it must be remembered that if physical activity *is* a major factor possible differences in physical activity *outside* of work must also be considered Certain tests of the physical activity explanation do not superficially at least, seem to provide consistency Thus physicists can be divided into two groups the theoretical physicists and the experimentalists It would be expected on the average that the experimental physicists have a greater degree of physical activity in their occupation than do the theorists Yet the 45 theoretical physicists in the overall group of physicists showed an average Atherogenic Index of 65 1 units whereas the 182 experimental physicists showed an average Atherogenic Index of 70 5 units This is in the opposite direction from the expectations based upon physical activity of occupation alone as the basis for the observations

In the main it does appear that the data concerning Atherogenic Index values for various occupations is consistent with the concept that physical activity at work is an important determinant but that in selected groups other factors may operate to distort

this relationship The findings are also in the main *consistent* with Morris hypothesis that the physical activity of certain occupations is a protective factor against development of clinical coronary heart disease The observations of a relationship between occupations and Atherogenic Index values need extensive broadening and understanding for this area may provide a major clue to understanding one basis for the relationship of occupation with incidence rate of coronary heart disease

TABLE LII

DIASTOLIC BLOOD PRESSURES IN TWENTY NINE OCCUPATIONAL CATEGORIES IN ONE INDUSTRY

Occupational Category	*Number of Men*	*Mean Age (years)*	*Diastolic Blood Pressure in mm Hg (adjusted to 35.0 years)*
Painters	1/	41 2	/9 7
Firemen	19	36 5	/3 6
Carpenters	91	3 4	~3 1
Machinist and Machinists Helpers	74	37 4	/2.9
Clerks	-3	32 3	??
Tool and Die Makers	62	36 0	/? 1
Custodians	50	49 1	71.5
Draftsmen	110	33 1	/1 4
Journeyman Machinists		36 9	71 4
Truck and Bus Drivers	?4	33 6	/1 4
Electronic Technicians	1/0	32.6	71.3
Mathematicians	61	?8 3	71 3
Storekeepers	30	3?.2	71.3
Computer and Duplicating Machine Operators	?4	31 1	71.2
Chemists	77	31.2	71 0
Physicists	7	30 6	0 9
Steamfitters and Boiler Operators	21	43.2	/0 9
Engineers	?76	3? 4	/0 9
Mechanical Technicians	90	34 8	/0.5
Accelerator Operators	D	31 4	/0 4
Police Officers	105	41 4	/0.3
Executives (Junior and A t ant Classification)	68	36 3	0.2
Buyers	33	38 0	/0 2
Electrician	43	36 7	69 8
Laboratory Technicians	47	31 ,	69.5
Laborers	40	39 9	69 1
Sheet Metal Workers	?2	43.2	69.?
Riggers and Equipment Movers	10	36 3	69 1
Welders	14	39 4	66 3

(b) Diastolic Blood Pressure and Occupation

The diastolic blood pressures were routinely measured for the same group of 1883 men whose Atherogenic Index values were determined The mean diastolic blood pressures, adjusted for the small age differences to an age of 35 0 years are presented in Table LII The only outstandingly high occupational group on the diastolic blood pressure scale are the painters Statistical test indicates that there is less than one chance in one hundred that the extent of elevation observed would arise by sampling alone No other single occupational category can be proved to show diastolic blood pressures higher than the group as a whole On the low side no single occupational category can be proved to show diastolic blood pressures different from the group as a whole In general the means of the diastolic blood pressure show less spread than the means of the Atherogenic Index values for the different occupational categories It does not appear therefore that variation of blood pressure with occupational category can help appreciably to account for variation in incidence rate of coronary heart disease However the pressures recorded here are taken after reclining 10 minutes It cannot be stated therefore that members of certain occupational categories do not show episodic diastolic blood pressure elevations of consequence even though their sustained diastolic pressures are not unusual

OCCUPATIONAL "STRESS" AND ATHEROGENIC INDEX VALUES

Several recent publications[89 to 91] have referred to effects of emotional and occupational stress upon blood lipid levels The occupational categories described above have been subjected to preliminary analysis difficult as evaluation is in this area for effects of such factors as job responsibility and demands upon Atherogenic Index values From all the occupational categories together those individuals were selected out who are listed on personnel records as supervisors foremen and coordinators all of which are positions of special responsibility The mean Atherogenic Index for the entire group of 62 such men was found to be

68 6 units contrasted with 69 1 units for the overall group of 1883 men There is therefore no suggestion here that responsibility positions are characterized by any features that tend to elevate blood lipid values As another test of the effect of responsibility of position the entire group of engineers (one of the largest single categories available for analysis) was divided into subgroups based upon their official professional ratings Higher professional ratings are accompanied by increased responsibility increased demands and a higher income After adjustment of the Atherogenic Index values to 35 0 years of age for all the professional rating groups (since the higher rating groups were slightly older than those of lower rating) no significant difference was found to exist between engineers with the lowest professional ratings for those with intermediary ratings or for those with the highest professional ratings If such factors as responsibility demands and frustration are really of consequence with respect to blood lipid levels then it appears clear that currently reasonable approaches to measuring such stress features are inadequate to allow for discerning effects

THE DIETARY BASIS FOR SO-CALLED OCCUPATIONAL "STRESS" EFFECTS

Friedman Rosenman and Carroll have recently reported[9] on changes in the serum cholesterol level purported to be the result of cyclic occupational stress in accountants a stress they referred to as socioeconomic stress This stress was described by them as a particular and rather specific type of emotional activity namely that concerned with excessive drive competition meeting *deadlines* and economic frustration They were trying to study a form of stress further described by them as one which imposed a sense of urgency upon the subjects It is of interest to note the basis upon which these authors selected this particular form of *stress* Having convinced themselves that socioeconomic stress was correlated with the incidence of clinical coronary heart disease they wanted to find out what kind of socioeconomic stress might be of importance They therefore interviewed by questionnaire 162 executives of a large oil com

pany a railroad company, and 3 advertising agencies plus 47 physicians actually treating cardiac patients. Since approximately 70% of both the lay and professional group chose the description of "socioeconomic stress" alluded to above, these investigators felt this must be the type worthy of study with respect to pathogenesis of clinical coronary heart disease. While this is a novel technique for deciding the probable etiology of disease, it is of interest to examine critically the far-reaching conclusions arrived at by these workers, for even accidental approaches to many problems have often led to highly important findings. Accountants were chosen as subjects because there existed, according to these investigators, a *socioeconomic stress* in these men predictably phasic enough during the first 5 months of the calendar year to allow periods of respite for control observation.

The *period from April 2 to April 15 was considered by* Friedman and co-workers to represent "severe stress," whereas May 14 to May 21 a period of "maximal respite" from stress. In all, 39 accountants participated in the study throughout the entire period. From the data presented by these workers the following are the mean serum cholesterol levels for "Maximal occupational stress" and for "maximal respite":

During "Maximal Occupational Stress" Mean Cholesterol =	230 mg/100ml
During "Maximal Respite" Mean Cholesterol =	222 mg/100ml
Difference	8 mg/100ml

In order to evaluate whether or not dietary changes during these periods might have accounted for the serum cholesterol difference shown above, these workers took a very detailed dietary history for the two critical periods: April 2-9 ("maximal stress") and May 14-21 ("maximal respite"). Since so much reliance is placed upon these dietary records by the authors, our first approach must be to accept the dietary evaluations at face value and to determine whether they support the conclusion arrived at that stress itself, rather than dietary changes, was responsible for the observation of a change in mean cholesterol level of 8 mg/100ml. The accountants were divided into two groups depending upon the type of accounting they did. Dietary evaluations were presented by Friedman and associates for

maximal respite and maximal stress The mean number of calories taken in daily for the combined group of 39 accountants during maximal stress was 1845 calories whereas during maximal respite it was 1783 calories Therefore at face value the accountants ingested 63 fewer calories per day during maximal respite then they did during maximal stress This caloric difference the investigators stated could not possibly have accounted for the 8 mg/100ml change in serum cholesterol upon which their thesis rests Is this true? Friedman and associates made no effort whatever to test whether this caloric change could or could not explain the 8 mg/100ml change in cholesterol level Instead they simply stated that it could *not* But there do exist ample dietary data to test this issue quantitatively

In the discussion of overweight and alterations of overweight a natural experiment was described in which 374 subjects were studied twice at approximately one and one half year intervals Those who lost weight showed lowering of S_f0 12 S_f12 20 S_f20 100 and S_f100-400 lipoprotein levels whereas those who gained weight showed increases in the levels of all these lipoproteins Those who did not change in weight did not change significantly in lipoproteins Taking all those data together we have the following straight forward estimations

For 1 pound of weight loss in a time interval *of* 62 4 weeks

the mean fall in S_f0 12 lipoprotein level = 1 5 mg
the mean fall in S_f12 20 lipoprotein level = 0 4 mg
the mean fall in S_f20 100 lipoprotein level = 1 7 mg
the mean fall in S_f100-400 lipoprotein level = 2 1 mg

In that observation period subjects were gaining or losing weight at various rates some over the entire 62 4 week interval others undoubtedly over a small fraction of that interval Most of the subjects did not even know their weight was changing The *average* rate of caloric restriction to lose one pound of weight in 62 4 weeks is estimated as follows Allowing for some water in body fat it requires a restriction of approximately 4000 calories to lose one pound of weight If this is to be lost on the average in 62 4 weeks *the daily caloric* restriction must be 4000 over 62 4x7 or 9 2 calories per day This number of calories restricted per day must therefore account for the falls in

pany a railroad company and 3 advertising agencies plus 47 physicians 'actually treating cardiac patients Since approximately 70% of both the lay and professional group chose the description of socioeconomic stress alluded to above these investigators felt this must be the type worthy of study with respect to pathogenesis of clinical coronary heart disease While this is a novel technique for deciding the probable etiology of disease it is of interest to examine critically the far reaching conclusions arrived at by these workers for even accidental approaches to many problems have often led to highly important findings Accountants were chosen as subjects because there existed according to these investigators a socioeconomic stress in these men predictably phasic enough during the first 5 months of the calendar year to allow periods of respite for control observation

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Indeed the dietary changes could readily have accounted for twice the observed changes In summary therefore the conclusion of Friedman and associates that the present studies indicate an extreme sensitivity of the serum cholesterol to the occurrence of emotional duress described as *socioeconomic stress* might much better be replaced with the conclusion that accountants eat a little more when they are working long hours and that possibly their cholesterol levels rise a little during such times in an amount expected from the extent of their dietary change

What other observations are in the literature which claim to relate stress with serum cholesterol or other lipid levels are no more convincing than those just discussed No critical evaluation of the quantitative changes observed and the extent to which they can be explained by concomitant dietary alteration is generally presented Thus the singling out of a few persons from a large group who show an appreciable change of serum cholesterol or lipoprotein level during an episode of presumed stress may very well reflect the singling out of the persons from the overall group who are most sensitive to relatively small dietary changes since it is well known that such persons exist

No acceptable evidence has yet been presented to suggest an effect of stress upon serum lipoproteins or serum cholesterol levels in man that cannot be as well or better explained by the solidly-established effects of dietary alterations upon such blood lipids It is to be hoped that some evaluation of the possible factor of stress will be made in the future

the various lipoproteins listed above This information can therefore now be put on a caloric basis as follows

For a restriction of 10 calories per day, the average fall in *lipoprotein levels anticipated are*

1 64 mg/100ml of s_f0 12 lipoproteins
0 44 mg/100ml of s_f12 20 *lipoproteins*
1 85 mg/100ml of s_f20 100 lipoproteins
2 29 mg/100ml of s_f100 400 lipoproteins

The chemical composition of these lipoprotein classes is known from the work of Lindgren and associates[35] The s_f0 12 and *s_f12 20 lipoproteins contain approximately 34%* cholesterol by weight the s_f20 100 and s_f100-400 contain approximately 13% cholesterol by weight Therefore the overall fall in serum cholesterol level corresponding to a 10 calorie per day restriction would be anticipated to be 1 64x0 34 + 0 44x0 34 + 1 85x0 13 + *2 29x0 13 or a total of 1 25 mg/100ml* This is of course the *average* fall anticipated some more sensitive than average showing a more extensive fall in level others less sensitive than average showing a less extensive fall (even including some with no change or a rise in cholesterol level)

Utilizing this simple *estimate (which is extremely unlikely* to be off as much as a factor or two) it can be determined how much the Friedman accountants should have fallen in serum cholesterol level as a result of ingesting 63 fewer calories per day during maximal respite than they did during maximal stress If 10 calories per day results in a fall of 1 25 mg/100ml of serum cholesterol then 63 calories would be expected to cause a fall of 6 3x1 25 or 7 9 mg/100ml of serum cholesterol This *is to be compared with the 8 mg/100ml fall in cholesterol* observed by Friedman and associates In actual fact the 8 mg/100ml serum cholesterol fall observed by Friedman is so uncertain statistically that it might really be 0 mg/100ml or as much as 16 mg/100ml just on a sampling basis alone The 63 calorie per day change in dietary consumption for the two periods stress and respite from stress can easily have been from 0 calories to 100 or more calories per day considering the strength of the information *provided Therefore the dietary changes* involved can easily have accounted for the observed cholesterol changes

ease Coronary heart disease at the sub-clinical level occurs in two types of individuals

(a) those who have never had an episode of clinical coronary heart disease They are developing sub-clinical coronary heart disease some at greater rates some at lesser rates and therefore have a greater or lesser risk of evolution of the clinical manifestations in such forms as angina pectoris myocardial infarction coronary insufficiency heart failure or death

(b) those individuals who have had a clinical manifestation of coronary heart disease in one or another form but who during the interim period after recovery from a first second or third clinical manifestation can again be regarded as being in the sub-clinical phase of the disease awaiting the possibility of a recurrence of the clinical entities

Both such groups of individuals deserve the attention of the clinician with respect to the prevention of future clinical manifestations of coronary heart disease Who are these individuals It has been stressed before that for group (a) *every adult in the population* is a potential candidate for future coronary heart disease Therefore every adult in the population may be regarded as a proper patient for the treatment of sub-clinical coronary heart disease and prevention of future clinical heart disease Indeed unless every adult in the population is regarded as a patient in this sense serious inroads upon the mortality now claimed by coronary heart disease in its various forms will not be made Patients in the second category group (b) namely those who have already had at least one clinical manifestation of coronary heart disease but who are now in the sub clinical phase again are self evident The vast majority of these will have been under the care of a physician who of course will know that they are again in the sub-clinical phase of coronary heart disease It would be deplorable to consider such patients simply as candidates for watchful waiting until a next episode of clinical coronary heart disease or to limit advice to them to a statement that no problem exists because they have weathered their acute clinical episode A great deal should be done for these patients and can be done without fear of provoking cardiac neurosis Our survey in this book of features associated with

Chapter XV

THE PREVENTION OF CLINICAL CORONARY HEART DISEASE

MANY FACETS of the problems of sub clinical coronary heart disease and the risk of future clinical manifestations have been taken up in this text Wherever the information was deemed pertinent to the clinical task of prevention and management of coronary heart disease this was emphasized It is the purpose of this chapter to pull together much of this information and to indicate to the clinician that an integrated program is possible today with which a highly promising effort can be made to prevent coronary heart disease The discussions which have preceded this chapter make it abundantly clear that our knowledge of coronary heart disease is not complete It is doubtful that for coronary disease or any other disease knowledge ever will be truly *complete* But for any disease the more facts that are at our disposal the more we know about the determinants of risk of the disease the course of the disease and about agents which influence one or another factors known to be involved in the disease the more it becomes possible to design a reasonable program for prevention of that disease So long as the clinician keeps an open mind with respect to the place of additional new laboratory and clinical findings the preventive program can be modified toward improvement In the introduction to this book it was stated that the management of clinical episodes of coronary heart disease is well covered elsewhere and is therefore not considered here What does deserve intensive practical consideration here is a program for applying extensive knowledge that is available and on a very solid footing toward the end of minimizing the rate of progression of sub-clinical coronary heart dis

genic Index elevation have much higher risks of future coronary heart disease than those characterizing an appreciable proportion of the men in the population It would seem completely unwarranted to exclude these women from our program of preventive management even though it is true that *on the average*, women have a lower coronary heart disease incidence rate than do men Going further one might choose to focus attention upon individuals over 50 years of age since the attack rate of clinical coronary heart disease is much greater above that age than it is on the average below that age and it continues to rise progressively with further increase in age In one sense concentration upon the over 50 year age group is justified by that fact of a higher attack rate of clinical disease *However two major* considerations militate against this type of approach First the incidence of clinical coronary heart disease is alarmingly high for persons below 50 years of age It is especially desirable to intercept such great prematurity of this disease Since risks can be predicted long in advance of clinical disease it would be particularly tragic to allow markedly excessive risks to go unnoticed and to be productive of manifest coronary heart disease below the age of 50 years These considerations argue strongly against the exclusion of *young* adults from the heart disease prevention program There are the many children who are characterized by massive lipoprotein level elevation because of hereditary defects in lipoprotein transport Unless some effort is really made to seek them out and to alter their lipoprotein levels their outlook is distinctly unfavorable Perhaps an even more cogent consideration in this regard *is* the fact that all of the evidence concerning the mode of *operation* of the lipoprotein level and the blood pressure in the *production* of an excessive rate of development of sub-clinical coronary heart disease points strongly to *an accumulative process* The longer this process goes on the more disease there will be and since we cannot count on the exact extent of reversal of established disease that may be possible this argues strongly in favor of a very early approach to determine the rate at which sub-clinical coronary heart disease is developing and to intercept its development before the total accumulated disease has become too great What

increase or decrease in the incidence rate of clinical coronary heart disease has demonstrated that such effects are mediated in the main either by the habitual level in the blood of certain lipoproteins the S_f0 12 S_f12 20, S_f20 100 and S_f100 400 lipo proteins, or by the blood pressure, or by both One factor that has not been treated here is that of coagulability of the blood and its relationship to at least some of the clinically manifest forms of coronary heart disease This is no oversight, but rather the result of the sketchiness of real evidence concerning the place of blood coagulability in the development of sub-clinical coro nary heart disease Some aspects of this problem will be con sidered below

There is every reason to believe that vigorous attention to these two factors the blood lipoproteins and the blood pressure can and will make a real difference in the mortality rate of coro nary heart disease Asymptomatic elevation in blood lipopro tein levels and hence of Atherogenic Index Value should not be regarded as innocuous The *absence* of symptoms characterizes the subclinical phase of coronary heart disease However the risk of future clinical manifestations is high with elevation in Atherogenic Index values and with the passage of time such high risk individuals will experience all too many clinical episodes of coronary heart disease Neither should asymptomatic elevation *of the blood pressure be regarded as benign, as it* has been by some workers either in men or women Asymptomatic eleva tion in blood pressure means on the average an increased rate *of accumulation of sub-clinical coronary heart dis*ease and an ultimate high risk of evolution into one of its serious or fatal clinical manifestations

Let us suppose one thinks of potential candidates for preven tion of clinical coronary heart disease among adults in the United States population Since men at most ages show a higher inci dence rate of clinical coronary heart *disease than do women* an initial conclusion would be that preventive medical attention should be centered upon men To be sure the attack rate is greater in the men so that in one sense *they are as a group in* greater need of preventive management But there are *many* women who either because of blood pressure elevation or Athero

tive prosecution of a program for the prevention of clinical coronary heart disease At present a major consideration is the low degree of reliability of the values determined by many clinical laboratories as recently reported[93] to say nothing of the methodology and standardization differences that exist from laboratory to laboratory But were this the real essence of the difficulty with the application of the blood cholesterol measurement steps could be taken to improve the existing situation Methodology could be standardized and valid reproducible techniques could be learned by essentially all clinical laboratories However even perfectly executed the measurement of the blood cholesterol will fall far short of provision of the requisite information *either* for prediction or for preventive management programs This does not mean that a blood cholesterol determination is without value Any biochemical measurement properly performed has intrinsic value but the issue of real consequence is whether or not the measurement provides the necessary clinical information It is certainly true that the blood cholesterol level is related to the development of coronary heart disease Furthermore during the sub-clinical phase of coronary heart disease elevation of blood cholesterol level is predictive of an increased risk of future clinical coronary heart disease But for prediction of risk even a perfectly executed blood cholesterol determination necessarily leads frequently to an erroneous answer concerning the patient Why is this so? The lipoproteins which circulate in the blood *all* contain some cholesterol Indeed the blood lipoproteins are essentially the sole source of what cholesterol is measured in a usual blood cholesterol analysis However two points concerning the blood lipoproteins and the cholesterol they contain are central to the entire problem These are the facts that

(1) only *certain* of the blood lipoproteins are important for coronary heart disease

(2) the content of cholesterol differs from the various lipoprotein classes

all this leads up to is the fact that no program can be regarded as medically sound if it falls short of doing two things providing the earliest possible evaluation of the lipoprotein status and blood pressure status of young adults preferably in the age bracket of 20 25 years At this age an appreciable number of individuals with high risk will be discovered Prevention has meaning for these individuals at that early age For those who are found to show a low risk during the third decade of life are most likely to retain this favorable status although in some instances there will be unexpected derangement of the lipoprotein levels and/or of the blood pressure as they grow older This latter group of individuals deserves a re check of status at intervals perhaps of three to five years throughout adult life

Sphygmomanometry is readily available to every physician in his office It is of little moment whether he measures blood pressure in a reclining versus a sitting position or with certain types of tolerance tests What is important is that some set of reproducible conditions be achieved for the periodic blood pressure check It is evident of course that multiple blood pressure determinations will greatly improve the accuracy of placement of an individual on a risk scale with respect to the blood pressure Very little is solved by the negative statement that blood pressure levels are variable for a single individual due to a variety of circumstances All experienced physicians know that they can by repeat determination get to know which persons show significant average trends toward elevation in the blood pressure level

The measurement of the blood lipoprotein levels and the Atherogenic Index value is also routinely available to physicians performed by methods that have been rigorously evaluated in over 150 000 determinations No doubt some clinicians will wonder whether one of the more simple blood lipid measurements might not serve as well as a determination of the actual lipoproteins involved in the development of coronary heart disease One such that comes into consideration is the determination of the blood cholesterol level Numerous major reasons exist which make it evident that such a determination of the blood cholesterol level will not provide the requisite information for the effec

Using some representative numbers consider one person with 400 mg/100ml of the high-density lipoproteins and another with 200 mg/100ml of these lipoproteins all other lipoprotein classes being equal Since the high-density lipoproteins are 13% cholesterol by weight the person whose blood shows 400 mg/100ml of high density lipoprotein will have 400x0 13 or 52 mg/100ml of cholesterol in the blood in this form The person with 200 mg/100ml of high-density lipoprotein will have 200x0 13 = 26 mg/100ml of cholesterol in the blood in this form The blood cholesterol analysis will show the former person to be 26 mg/100 ml higher than the latter and would predict the former person to have a higher risk of coronary heart disease when in fact the s_f0 400 lipoproteins may be identical in level the Atherogenic Index values are therefore identical and the predicted risk of coronary heart disease will be identical

A much more serious error can arise in another way through reliance upon the blood cholesterol level without knowledge of the lipoprotein distribution Suppose two men at age 35 years are considered with the following lipoprotein distributions

	Case A	Base F
s_f0 12	400 mg/100ml	400 mg/100ml
s_f12 20	50 m /100ml	50 mg/100ml
s_f20 400	300 mg/100ml	100 mg/100ml
High Density Lipoprotein	100 mg/100ml	98 mg/100ml

The s_f0 20 lipoproteins are approximately 34% cholesterol by weight the s_f20 400 lipoproteins 13% cholesterol by weight and the high density lipoproteins 13% cholesterol by weight These three classes together provide almost all of the blood cholesterol Therefore for case A the blood cholesterol is (450) x (0 34) plus (300) (0 13) + 100 (0 13) which is 205 mg/100ml For case B the blood cholesterol is (450) (0 34) + (100) (0 13) + 300 (0 13) which is 205 mg/100ml Therefore on the basis of blood cholesterol determination Case A and Case B would be stated to have identical risks of coronary heart disease Now the Atherogenic Index may be calculated for both cases For Case A the Atherogenic Index is (1 0) (400) + (1 75) (350) over 10 or 101 units For Case B the Atherogenic Index is (1 0) (400) + (1 75) (150) over 10 or 66 units

THE IMPORTANCE OF THE FACT THAT ONLY CERTAIN LIPOPROTEINS ARE INVOLVED IN CORONARY HEART DISEASE

The blood lipoproteins can be broadly characterized as belonging to three major groups

(a) The s_f0-400 band of *lipoproteins of demonstrated im*portance for coronary heart disease (See Chapter III)

(b) The very large lipoproteins from *s_f400 out to the chylomicrons For the human these have not been demon*strated to be of importance for coronary heart disease although it has not been demonstrated that they are innocuous * Fortunately such lipoproteins are not often very high in level and secondly their levels correlate so highly with those of the s_f100-400 class that *information concerning them is available when the* s_f100-400 class is measured

(c) The high density lipoproteins which are comparable in part *to those referred to as alpha* lipoproteins by techniques other than ultracentrifugation Such lipoproteins are definitely *not* elevated in level in coronary heart disease In fact what data are available indicate that they are depressed slightly in level in coronary heart disease[94, 9]

The major goal of a blood lipid measurement with *respect* to prediction of coronary heart disease risk is to assess the amount of lipid in the blood in the form of lipoproteins in the flotation classes between s_f0 and s_f400 It was stated above that the high density lipoproteins are unimportant for coronary heart disease However these lipoproteins *do* contain cholesterol to the extent of approximately 13% by weight There is considerable variation from one person to another in the level of these high density lipoproteins and they are almost completely independent of the level of the various lipoprotein classes from s_f0 to s_f400 Therefore it is readily possible to find two humans of the same age and sex in one of *whom the high-density lipo*proteins are twice as high in level as in the other but where every lipoprotein from s_f0 to s_f400 is the same for both persons

*In experimental animal studies e g in the rabbit the very large lipoproteins are innocuous with respect to arteriosclerosis development in comparison with those comparable in size with human s_f0-400 lipoproteins

	Case 1 (mg/100ml)	Case 2 (mg/100ml)	Case 3 (mg/100ml)
Cholesterol Contributed From High Density Lipoproteins	300x0 13=39	300x0 13=39	300x0 13=*9
From s_f12 20 Lipoproteins	60x0 34= 0	60x0.34=20	60x0.34=?0
From s_f0 12 Lipoproteins	400x0.34=136	300x0 34=102	200x0 34=68
From s_f20 400 Lipoproteins	100x0 13=13	200x0 13= 6	300x0 13 -39
Total Blood Cholesterol	204	187	166
Atherogenic Index	68 units	76 units	83 units

Here the paradoxical situation arises that the cholesterol dropping successively from Case 1 to Case 3 predicts erroneously a successively lower risk of future clinical coronary heart disease whereas the Atherogenic Index rising successively from Case 1 to Case 3 predicts a successively higher risk of future clinical coronary heart disease The source of erroneous prediction from the cholesterol measurement arises from the shift of lipoproteins relatively rich in cholesterol to lipoproteins relatively poor in cholesterol content Hence the cholesterol level falls However the cholesterol poor s_f20-400 lipoproteins are even more important milligram for milligram than the s_f0 12 lipoproteins Hence it is possible to have the Atherogenic Index rise as the cholesterol level falls! Levels such as are shown for Case 1 and Case 3 can be seen in a single individual during therapy Suppose that a man started with a distribution of lipoproteins identical with that of Case 1 If a regimen of a low animal fat high carbohydrate diet were instituted the s_f0 12 lipoproteins will fall in general and the s_f20-400 lipoproteins will rise Cases have been observed where these changes could convert a distribution such as that of Case 1 to that of Case 3 Thus the cholesterol measurement before and after institution of the dietary therapy would indicate erroneously a favorable response whereas the lipoprotein Atherogenic Index measurement would indicate an unfavor

The risk evaluation from Table XV is that the man with the Atherogenic Index value of 101 units has 14.2 over 3.24, or 4.4 times the risk of future clinical coronary heart disease that characterizes the man with an Atherogenic Index of 66 units. Thus in these two cases the blood cholesterol measurement (even if performed perfectly) is off 4.4 times in its prediction of equal risk for the two men whose cholesterol levels are both 205 mg/100ml. This cholesterol level of 205 mg/100ml is a relatively low one. Hence a favorable prediction would be made on this basis. Yet one of the two men described with this cholesterol level has a highly unfavorable outlook and is in need of preventive medical management, a fact which would be lost sight of entirely if attention were focussed upon the low cholesterol level.

THE IMPORTANCE OF THE FACT THAT LIPOPROTEINS DIFFER IN CHEMICAL COMPOSITION

In the illustrations above the obscuring effect of the high density lipoproteins upon the prediction via blood cholesterol measurement was described. Another type of difficulty operates to lead to erroneous prediction through blood cholesterol measurement, namely the differing chemical composition of lipoproteins within the S_f0 to S_f400 band. Three men may be considered with identical levels of the high density lipoproteins, e.g. 300 mg/100ml. Now various possible (and observed) combinations of S_f0-12, S_f12-20 and S_f20-400 lipoproteins may be considered. Suppose for simplification S_f12-20 remains at 60 mg/100ml for all the cases to be analyzed. Suppose further that for S_f0-12 plus S_f20-400 there is a total of 500 mg/100ml. Three distributions within this level of 500 mg/100ml will illustrate the problem. Let the first case (Case 1) have S_f0-12 = 400 mg/100ml and S_f20-400 = 100 mg/100ml, the second case (Case 2) have S_f0-12 = 300 mg/100ml and S_f20-400 = 200 mg/100ml and the third case (Case 3) have 200 mg/100ml of S_f0-12 lipoproteins and 300 mg/100ml of S_f20-400 lipoproteins. Now from chemical composition data for the various lipoproteins, the blood cholesterol can be calculated for cases 1, 2 and 3 and from the S_f0-12, S_f12-20 and S_f20-400 the Atherogenic Index is calculated.

genic Index should be lowered These are hypothyroidism and diabetes mellitus

Hypothyroidism should be searched for carefully and should be treated effectively where present for the elevation of S_f0 12 and S_f12 20 lipoproteins means an elevation in the Atherogenic Index and thereby an increase in the risk of clinical coronary heart disease Fortunately therapy with desiccated thyroid sub stance thyroxine or tri iodo thyronine is specific therapy and will effect a lowering in lipoprotein level as a concomitant of correc tion of the hypothyroidism Some patients present more occult problems referable to the thyroid status Where clinical hypothy roidism is suspected as a possible diagnosis and where S_f0 20 lipoproteins are elevated but where other laboratory measure ments of thyroid function are equivocal a trial of thyroid ther apy is clearly indicated There are further a large number of persons in the population who at one time or another have had ablative treatment of their thyroid gland by surgery radiation or by chemical means To be sure frank clinical myxedema is not a common residual effect of surgical treatment of hyperthyroid ism Nevertheless persons who have had ablative therapy to their thyroid may suffer elevation of S_f0 12 and S_f12 20 lipo protein levels Even in the absence of clinical hypothyroidism such persons deserve a trial of thyroid replacement therapy

Diabetes mellitus presents the second special situation of real consequence Of course first of all diabetes itself must be controlled clinically Thereafter attention must be directed toward any excessive risk of coronary heart disease a particular diabetic may have as a result of lipoprotein Atherogenic Index elevation The discussion of diabetes in Chapter XII and the data of Table XLV indicate strongly that chemical control of diabetes (even within the clinical state free of acidosis) is of real importance in determination of the lipoprotein status There fore within the limits imposed by patient intelligence life cir cumstances and the prevention of hypoglycemic episodes hyper glycemia and glycosuria should be minimized The evidence in Table XLV gives the average improvement in Atherogenic Index values with increase in the control of hyperglycemia It follows that some diabetics will experience much greater than average

able response which is correct The use of the familiar rice diet is a case in point, where precisely this type of situation arises and where the blood cholesterol would indicate the direction of the response *opposite* to what is truly occurring in the patient *Probably the major reason why this type of patient on a rice* diet does not fare as badly on the average as the Atherogenic Index trends would suggest, is that the rice diet regimen as practised is associated with a favorable fall in diastolic blood pressure

THE PLANNING OF A PREVENTIVE REGIMEN FOR INDIVIDUAL PATIENTS

For those patients whose overall risk of coronary heart disease is low or moderate when calculated by multiplication of the risk arising from Atherogenic Index value by that arising from diastolic blood pressure the best program is simple notification of the patient that he is a fortunate person characterized by a low risk of future coronary heart disease No specific measures are indicated *Where the overall risk is elevated from elevated* blood pressure with or without Atherogenic Index elevation it is definitely indicated that a program be directed toward lowering such elevated blood pressure This is true even though the blood pressure elevation is asymptomatic at the time of study The entire subject of the most efficacious procedures for controlling elevation in blood pressure is a major subject in itself a subject covered elsewhere in sources available to physicians Where the risk is elevated from elevation in Atherogenic Index with or without diastolic blood pressure elevation there is a definite indication for a program directed toward the lowering of the elevated Atherogenic Index values The approach to this problem for an individual patient deserves amplification

THE PROGRAM FOR LOWERING ELEVATED ATHEROGENIC INDEX VALUES

Special Situations

Two special situations must be commented upon before consideration of the person in the population at large whose Athero

DIETARY APPROACH TO ATHEROGENIC INDEX LOWERING IN THE OVERWEIGHT PERSON

The overweight person shows, on the average an appreciable elevation of the Atherogenic Index value (See Chapter IX) Further in those overweight persons who demonstrate elevation in blood lipoprotein levels and Atherogenic Index values the correction of overweight via a decrease in habitual calorie intake provokes a fall in Atherogenic Index value which is maintained if the person does not return to his habitually high calorie intake The natural experiment described in Chapter IX provides us with very reasonable working data for the clinician to use in planning a regimen for the overweight person Under the usual circumstances of living a cross-section of individuals described in Chapter IX either lost or gained weight spontaneously during a one to two year period The lipoproteins and Atherogenic Index increased on the average for those who gained weight and decreased on the average for those who lost weight From these data the average changes in level that can be anticipated for the various lipoprotein classes and for the Atherogenic Index value per unit change in daily calorie intake were calculated (See Chapter XIV) These values are as follows

For a reduction of 10 calories per day in habitual caloric intake *on the average*

S_f 0 12 lipoprotein levels fall	1 6 mg/100ml
S_f 12 20 lipoprotein levels fall	0 4 mg/100ml
S_f 20 100 lipoprotein levels fall	1 8 mg/100ml
S_f 100-400 lipoprotein levels fall	[illegible] 3 mg/100ml
Atherogenic Index Values fall	0 95 units

The clinician may utilize such data directly in planning a long term regimen for the overweight person This may be illustrated by consideration of a specific case of an overweight man of 35 years of age whose Atherogenic Index value is 120 units a value that corresponds to an appreciable elevation in risk of future clinical coronary heart disease The physician would be desirous of lowering such a value to 80 Atherogenic Index units if possible or perhaps more What caloric restriction is needed? If 10 calories per day corresponds to an average lowering in Atherogenic Index of 0 95 units then the required caloric restriction

effects upon Atherogenic Index value others much lesser effects The clinician can readily determine this in specific patients directly For those patients where more rigid control produces large drops in Atherogenic Index values advantage should be taken of this For those where the effect of control rigidity upon Atherogenic Index is minor the clinician may decide to relax control measures appreciably

General Cases

We come now to the general case of the person in the population at large whose Atherogenic Index is elevated and who is in need of medical management to lower the elevated value This person is free of such known metabolic disorders as hypothyroidism or diabetes mellitus which bring in special considerations A program of preventive medical management is needed for this person in the population at large At the present time *and with the knowledge now available to us dietary measures* are first in importance in part because of the widespread confirmation of their efficacy in achievement of Atherogenic Index lowering and in part because the dietary approach has so relatively few unknowns in the form of side effects that may characterize pharmaceutical approaches Where dietary measures fail to produce the desired effects upon blood lipoproteins either because the patient is metabolically unresponsive or because he is uncooperative with respect to the dietary measures there do now exist certain pharmaceutical agents to bolster the physician s armamentarium in this field Further pharmaceutical research, on a large scale is urgently to be encouraged for it is entirely reasonable to believe that an ultimate replacement of dietary by pharmaceutical methods is possible The dietary approach is best analyzed if patients are first categorized into those who are overweight and who should lose weight and those who are either at ideal weight or are underweight in which cases weight loss is undesirable

the calories that must be restricted either in the form of animal fat or carbohydrate (depending upon the lipoprotein distribution) by calories in the form of one of the innocuous vegetable oils

DIETARY APPROACH TO LOWERING OF ATHEROGENIC INDEX VALUES IN PERSONS AT IDEAL WEIGHT OR BELOW IDEAL WEIGHT

It has been adequately stressed that lipoprotein level and Atherogenic Index elevation are by no means limited to the over weight person Both may occur in persons at ideal weight or in persons who are underweight Calorie restriction will therefore be out of the question in these cases in general But calorie restriction is *not* essential to achieve lipoprotein lowering It was shown in the discussion of Chapter X that alteration in the *source* of calories can provoke marked lowering of lipoproteins From the data of Tables XXXVIII and XXXIX the following average responses can be estimated

For every gram per day of animal fat* restricted on the average

S_f 0 12 lipoprotein levels fall	1 3 mg/100ml
S_f 12 20 lipoprotein levels fall	0 7 mg/100ml
S_f 20 100 lipoprotein levels fall	negligibly
S_f 100 400 lipoprotein levels fall	negligibly

Similarly for every gram per day of carbohydrate restricted on the average

S_f 0 12 lipoprotein levels fall	negligibly
S_f 12 20 lipoprotein levels fall	negligibly
S_f 20 100 lipoprotein levels fall	0 1 mg/100ml
S_f 100 400 lipoprotein levels fall	0 35 mg/100ml

With the knowledge of the patient s lipoprotein distribution the dietary alterations can be *prescribed by the* physician as developed in the following illustrative examples

If a patient at ideal weight or below is characterized *primarily* by elevation in S_f 0 12 and S_f 12 20 lipoprotein levels restriction

* Direct data are not available for *saturated* vegetable fats in these same subjects From the general experience of workers in this area it would be safe to use the *same* values for saturated vegetable fat as for animal fat

to reduce the Atherogenic Index by 40 units is (40 over 0.095)×10 or 421 calories per day. Many overweight patients can well afford to ingest 421 fewer calories per day. The *maintenance* of the average drop of 40 units in Atherogenic Index value requires that this person's *habitual* caloric intake remain 421 calories per day fewer than before therapy. Whether a physician chooses to reduce weight in overweight patients rapidly or slowly is his own choice, but the important issue here is that over the long term this patient must still average 421 calories fewer per day to maintain the lowered Atherogenic Index value.

This is how the physician can start with the management of the overweight patient. Of course few patients are precisely average in their response. Therefore with a caloric restriction of 421 calories per day, some will show even a more marked drop in Atherogenic Index than the calculated 40 units, others a lesser response. No substitute for direct checking of response in each patient is currently known. If the response is much better than average for a particular patient, then the physician may wish to liberalize the regimen and make the habitual caloric restriction less than 421 calories per day. If the response is poorer than average, then two possible considerations arise:

(1) the patient simply is not responsive to dietary measures, or

(2) the patient needs more specific dietary measures than mixed calorie restriction.

The calculated responses to calorie restriction are for *mixed calorie restriction in persons with usual distributions of the various* lipoprotein classes which contribute to the Atherogenic Index. Since it is known that the S_f0-12 and S_f12-20 lipoprotein *levels are lowered by restriction of* animal fat and saturated vegetable fat and that S_f20-100 and S_f100-400 lipoprotein levels are lowered by carbohydrate restriction, the physician can take advantage *of these facts either in the overweight patient*, the ideal weight patient or the underweight patient. For example, the physician may be dealing with an overweight patient for whom he considers a habitual *reduction of 421* calories per day as *too* much. In this case, by specific attention to that patient's lipoprotein distribution, the physician may choose to replace some of

drate can be replaced by one of the acceptable vegetable oils without fear of elevation of any lipoprotein classes

These are the general principles which can guide the physician in planning a dietary regimen At all times it must be borne in mind that the particular patient's sensitivity to the various dietary factors is the ultimate guide for that patient But the general principles can be utilized to initiate the program of prevention These dietary alterations neither require liquid formula diets nor unpleasant fad dieting Endless variety is possible and is available for specific planning of kitchen tested menus and recipes within the framework of these dietary principles * Nor is there any indication to deviate from the sound nutritional principles concerning adequacy of protein mineral and vitamin intake The concern over deficiencies that might be encountered in alteration of diets is most commonly encountered from sources with little or no experience with dietary alteration Probably it would be best to refer to the diets to be utilized as altered diets rather than restricted diets for extensive experience with patients indicates that they are hardly experiencing any real restrictions when they alter their diet to one consistent with an effort to prevent coronary heart disease

PHARMACEUTICAL APPROACHES TO THE LOWERING OF ELEVATED LIPOPROTEIN LEVELS AND ATHEROGENIC INDEX VALUES

Dietary methods are highly effective in the lowering of lipoprotein Atherogenic Index values Yet even with careful application of the dietary methods available there will still be three classes of patients who present a problem These are (a) the patients who will not adhere to the dietary program even though its efficacy has been demonstrated (b) the patients who respond to diet but who are still in need of more extensive Atherogenic Index lowering and (c) the patients who respond poorly to dietary measures For all these individuals the availability of measures to supplement the dietary approach would be highly wel

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* *Dietary Prevention and Treatment of Heart Disease* by John W Gofman Alex V Nichols and E Virginia Dobbin G P Putnam's Sons 1958

of animal fat is indicated Suppose a patient shows an s_f0 12 level of 550 mg/100ml and an s_f12 20 lipoprotein level of 80 mg/100ml and that the physician would like to achieve a 20% lowering of both that is a lowering of s_f0 12 lipoproteins to 440 mg/100ml and a lowering of s_f12 20 lipoproteins to 64 mg/100ml The *lowering of animal fat intake for this extent of s_f0 12 lipo* protein level lowering is calculated as 110 over 1 3 or 84 6 grams per day on a habitual basis Many Americans consume considerably more than this amount of animal fat per day others do not If this much animal fat is available for restriction a corresponding weight of any of several vegetable oils such as corn oil cottonseed oil peanut oil or safflower oil can be incorporated in the diet thus averting *any* caloric loss and hence any weight loss Since these calculations are for *average* patients the physician will be very pleased with the much greater lipoprotein response in some patients and will realize that this approach alone is inadequate for certain other patients

If a patient at ideal weight is characterized by elevation in s_f20 400 lipoproteins the indications are in the direction of car*bohydrate restriction The data indicate a lesser sensitivity* of s_f20 100 lipoproteins to carbohydrate restriction than that for s_f100 400 lipoproteins Whether this is generally true or whether it represents a feature of this particular group of subjects is not known As a reasonable approximation it can be estimated that *s_f20-400* lipoproteins as an overall group fall some *0 2 mg/100ml* per gram of carbohydrate per day Suppose the *s_f20 400* lipo protein level is high and it is desired to achieve a reduction of 50 mg/100ml The required restriction of carbohydrates is 50 over 0 2 or 250 grams per day This is an appreciable reduction in carbohydrate intake per day and one not readily achieved in some patients Fortunately however patient with marked elevation in s_f20 100 lipoprotein levels are *much* more sensitive than average to the effect of carbohydrate and will show much more marked drops in level than the 0 2 mg/100ml per gram of dietary carbohydrate estimated above For them modest carbohydrate restriction will provoke appreciable falls in s_f20-400 lipo protein levels In other patients the effect of carbohydrate restriction will be much less The calories lost from carbohy

istration On the other hand the asymptomatic relatively youthful person with marked elevation in lipoprotein levels can be treated with thyroid substance under observation without any undue fear that unmanageable side reactions will develop In those unusual cases where real evidence of intolerance develops this fact itself decides the issue Thyroxine or tri iodothyronine are also effective in reduction of elevated lipoprotein levels[80, 81] There appear to exist few major features which would differentiate these with respect to efficacy from desiccated thyroid substance There is no reason known at this time why thyroid administration cannot be used as a supplement to dietary measures

Estrogenic Hormones

Interest in estrogenic hormones as possible pharmaceutical agents for reduction in elevated lipoprotein levels has been widespread[96, 97, 98, 99] There has existed no doubt concerning efficacy of estrogenic substances in effecting reduction in blood lipoprotein levels for some time now However in many of the studies the dosage levels employed were relatively enormous with the result that side reactions of sufficient severity were induced as to discourage further consideration of this class of substances by many physicians However certain of the studies have been carried out at more modest dosage levels with favorable effects upon blood lipoproteins[99, 100] One of these is a very long term study of the administration of ethinyl estradiol to male myocardial infarction survivors In that study Marmorston Moore and their associates have endeavored to adjust the dosage of ethinyl estradiol during the study for each patient in an effort to titrate the patients so that side reactions such as gynecomastia and loss of libido could be minimized or avoided entirely The median dose of ethinyl estradiol in their series of patients has been 100 micrograms per day administered orally These eighteen patients had been treated at least for 90 days The effect of ethinyl estradiol administration after 90 days showed several remarkable features Significant reductions occurred in mean level of all four lipoprotein classes S_f0-12 S_f12-20 S_f20-100 and S_f100-400 For the S_f12-20 S_f20-100 and S_f100-400 lipopro

come Myriads of pharmaceutical agents have been proposed for accomplishment of this task few have proved to have any merit But these few that have shown merit in that lipoprotein levels can often be reduced through their use deserve specific comment here

Thyroid Substance

Desiccated thyroid substance has been conclusively shown to be capable of provoking lipoprotein and Atherogenic Index lowering in euthyroid persons (See discussion in Chapter XIII) In the euthyroid adult the usual ultimate requirement for maintenance of a suppression of Atherogenic Index values is a dose of 3 grains or more per day of USP desiccated thyroid substance Smaller doses ultimately allow for escape mechanisms to operate as previously discussed There does appear to be some virtue in building the thyroid dosage up relatively slowly on a schedule such as one grain per day for two weeks then two grains per day for two weeks then three grains per day for four weeks At this point, a determination can be made of the efficacy of the program by an analysis of the blood lipoproteins If inadequate, then the dose should be increased to four grains per day for one to two additional months with subsequent blood lipoprotein determination Many physicians have maintained large numbers of patients on doses of four or more grains of thyroid substance per day over periods of years Thyroid substance most uniformly affects the s_f0 12 and s_f12 20 lipoprotein levels although less regularly it can also provoke marked lowering of s_f20 100 and s_f100 400 lipoprotein levels The relationship between extent of drop in levels with initial lipoprotein level is marked for all the lipoprotein classes (See Chapter XIII)

The problem of wisdom of use of an agent such as desiccated thyroid substance for the purpose of achievement of Atherogenic Index reduction is one where individual clinical judgments will differ widely As emphasized before the selection of candidates for the use of thyroid substance should in large measurement help determine the physician s attitude The patient with severe symptomatic clinical coronary disease in the form of angina pectoris is not likely to be considered for a trial of thyroid admin

mittent anticoagulation a combination of these effects or by some wholly separate mechanism needs further elucidation

Other Pharmaceutical Agents

Beta sitosterol[10, 106, 19] and nicotinic acid[108, 109, 110] have been studied by several workers with respect to effectiveness in reduction of serum cholesterol levels Adequate data concerning effects upon the various lipoprotein classes are not currently available Farquahar has suggested that beta sitosterol probably lowers the Sf0 10 lipoprotein class but no direct data were presented to substantiate this Unfortunately many studies with agents such as the sitosterols suffer from the failure of the investigators to control the variable of diet To what extent sitosterols are effective in lowering blood lipids and to what extent they are reflecting an altered dietary composition during their administration is by no means clear It is to be hoped that definitive evaluation of the lipoprotein response to nicotinic acid in the dosage range of 3 to 6 grams per day will soon be available Nicotinic acid amide is reported to be without effect upon blood lipid levels

teins, the effect of estrogen administration was more marked for those showing initially high levels of these lipoprotein classes. In the men with moderate or low levels of these lipoprotein classes, there appeared to be little effect of the estrogen administration. From the point of view of clinical application this is a favorable finding since it is precisely those individuals with the highest initial levels who are in greatest need of an agent to lower the levels. The relationship of response with initial lipoprotein level is analogous to that observed in the case of thyroid administration. The magnitude of reduction in lipoprotein levels and Atherogenic Index values in the Marmorston-Moore study is very large and hence most promising. Should the longer term follow-up continue to indicate such large effects and should the side reactions be of sufficiently low intensity, ethinyl estradiol in the dosage range used by these workers may prove to be a most valuable pharmaceutical aid in lowering elevated lipoprotein levels in men. Studies are in progress in women.

Heparin

Parenteral heparin administration is known to provoke an acute fall in the level of S_f 12-400 lipoprotein levels[101, 102, 103]. This fall is the result of the activation *in vivo* by heparin of a lipoprotein lipase which effects the hydrolysis of triglyceride contained in these lipoprotein classes. Unfortunately, however, the enzyme seems to remain activated approximately as long as appreciable heparin activity is present. Thus a single intravenous injection of sodium heparin can effect lipoprotein level reduction for a period of several hours. Subcutaneous injection of heparin will extend such periods considerably, but even in this case a single injection will depress S_f 12-400 lipoprotein levels for a period less than 24 hours. In a separate study of mortality among patients with established clinical coronary heart disease, Engelberg has reported a highly significant effect of intermittent subcutaneous heparin administration in the reduction of mortality over a two-year period in comparison with a placebo-treated control series[104]. Whether or not the reported mortality decrease operates via the intermittent reduction in lipoprotein level via inter-

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CONCLUSION

Coronary heart disease has been considered here in the light of modern laboratory and clinical evidence A reasonably consistent and integrated concept of some of the major aspects of this disease has it is hoped been developed This concept leads to a suggested program of positive measures that may be considered for the initiation of a program for the prevention of coronary heart disease during its sub clinical phase so as to minimize the risk of its evolution into the full blown clinical entity The available knowledge is far from complete With enormous progress in further clarification there will still remain significant voids in our knowledge But today an integrated framework of evidence does suggest that further delay in the application of a great fund of knowledge is no longer indicated Therapeutic nihilism is not the equivalent of a justifiable and well founded conservatism in medicine To be sure views will change as new evidence develops The major features however of the knowledge upon which a program of prevention is suggested are very solidly grounded and will not change appreciably It is not intended that biochemical or biophysical approaches to the management of sub clinical coronary heart disease be in any way considered as a replacement for the physician caring for a patient as a human Rather such approaches are intended to strengthen *the scientific basis underlying the clinician s approach to this* very serious medical problem So long as the physician can assure himself that the application of modern concepts to prevention of coronary heart disease will not be harmful and that a strong body of evidence indicates a very great likelihood that such application will be helpful it hardly could be considered radical *to start now rather than to wait* for complete agreement by everyone concerning every facet of this disease

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Chapter 12

HYPERTENSIVE RETINOPATHY

Bright[1] pointed out in his communication of 1836 that impairment of vision may be a symptom of renal disease. The visual defect may be due to various causes. Amaurosis occurs as a manifestation of hypertensive encephalopathy (p 348) the refracting media fundus and pupillary reflexes being normal. Hemorrhage into the retina, the media or the subconjunctival tissues may occur. Unusual cases of visual defects in hypertensive and arteriosclerotic patients are closures of the central artery or vein or large branches. But far more important than these vascular accidents are the peculiar retinal changes first observed anatomically by Tuerck in 1850 ophthalmoscopically by Heymann[3] in 1858 and termed albuminuric retinitis by Liebreich.[4]

The term albuminuric retinitis has been used almost universally until within recent years. It is however inappropriate and should be discarded for the following reasons.

1 The retinal lesions in question are not closely correlated with albuminuria. In the nephroses in which albuminuria is at a maximum the retinal changes do not occur and are unusual in the nephrotic type of glomerulonephritis. In the end stages of glomerulonephritis and essential hypertension where the retinal lesions are most common albuminuria may be slight and occasionally even absent. There is thus no necessary connection between proteinuria and retinal lesions in Bright's disease.

2 The lesions in the retina are not inflammatory in nature but result from circulatory or metabolic disturbances. The use of the word retinitis is therefore objectionable.

The available evidence indicates that the retinal lesions formerly included in the concept of albuminuric retinitis groups together three pathogenetically distinct types of retinopathy. These will be designated in accord with the essential factor in their pathogenesis.

1 *Hypertensive Retinopathy* —The classical picture of albuminuric retinitis occurs only in the presence of hypertension. It will be seen in the following that hypertension is the essential factor in the pathogenesis of the retinal changes.

2 *Arteriosclerotic Retinopathy* —In chronic Bright's disease there occur retinal lesions which result from retinal arteriosclerosis. While hypertension is most often present in these cases the same lesions may result from arteriosclerosis in the absence of elevated blood pressure.

3 *Diabetic Retinopathy* —There is a form of retinal change specifically due to diabetes. Because this retinal change is often associated with

proteinuria edema and the other features of the Kimmelstiel Wilson syndrome it was formerly included in "albuminuric retinitis" However diabetic retinal lesions have no necessary correlation with proteinuria hypertension or renal insufficiency and often precede the latter in the evolution of the full fledged Kimmelstiel Wilson syndrome Diabetic retinopathy is discussed on page 509

In any of these retinopathies the same changes in the retinal arteries may be present these will be discussed first

The Retinal Arteries in Hypertension —In at least the large majority of instances of pronounced hypertension the elevated blood pressure is reflected in the appearance of the retinal arteries Gowers[4] long ago observed that "When in chronic Bright s disease the pulse is incompressible there may as a rule be seen reduction in size of the retinal arteries independent of any retinal disease and this reduction in size is fairly proportionate to the increased arterial tension" This observation is all the more remarkable because it was made before the days of the sphygmomanometer In the vast majority of patients with marked hypertension the retinal arteries reveal one or more of such changes as narrowing irregularity of lumen pallor broadening of the reflex stripe a coppery or silvery appearance arteriovenous compression visibility of the arterial wall and tortuosity Leatham[6] found combinations of these changes which he regards as characteristic of hypertension in each of 45 patients with a diastolic pressure of 110 mm or more such "hypertensive arterioles" were not present in any of his 103 normotensive controls Roesler Gibson and Hussey[7] detected changes in the retinal arterioles in every one of 80 patients with uncomplicated essential hypertension Wagener[8] pointed out that the initial changes in the retinal arteries in hypertension are narrowing pallor of the entire width of the arterial blood column and accentuation of the reflex stripe In the experience of the writer it has been rare that the retinal arteries of a patient with pronounced hypertension are not narrowed Often indeed indubitable and sometimes pronounced narrowing of the retinal arteries is present in youthful sufferers from essential hypertension in whom the elevation in pressure is but modest and even intermittent The attenuation of the retinal arteries persists in hypertensives in whom the blood pressure has fallen after myocardial infarction In severe hypertension the narrowing is generally immediately obvious But in less marked hypertension the attenuation of the arteries may be only slight In estimating the caliber of the retinal arterioles they should be carefully compared to corresponding veins Normally the artery is about two-thirds to three-quarters as broad as the vein However one must be sure that the artery and the vein actually correspond often an artery is accompanied by two veins or vice versa or the branching different—all of which vitiate the comparison In old age the arteries are often narrow in the absence of hypertension

Both increased tone and arteriosclerotic thickening of the walls may participate in the thinning of the arterial blood columns in hypertension Dissociation of the contribution of these factors in the individual case may be difficult or impossible The nature of the case and the presence or absence of other evidence of retinal arteriosclerosis may help decide

Chapter

12

HYPERTENSIVE RETINOPATHY

BRIGHT[1] pointed out in his communication of 1836 that impairment of vision may be a symptom of renal disease. The visual defect may be due to various causes. Amaurosis occurs as a manifestation of hypertensive encephalopathy (p. 348), the refracting media, fundus and pupillary reflexes being normal. Hemorrhage into the retina, the media or the subconjunctival tissues may occur. Unusual cases of visual defects in hypertensive and arteriosclerotic patients are closures of the central artery or vein or large branches. But far more important than these vascular accidents are the peculiar retinal changes first observed anatomically by Turck in 1850, ophthalmoscopically by Heymann[3] in 1858, and termed albuminuric retinitis by Liebreich.[4]

The term albuminuric retinitis has been used almost universally until within recent years. It is, however, inappropriate and should be discarded for the following reasons:

1. The retinal lesions in question are not closely correlated with albuminuria. In the nephroses, in which albuminuria is at a maximum, the retinal changes do not occur, and are unusual in the nephrotic type of glomerulonephritis. In the end stages of glomerulonephritis and essential hypertension, where the retinal lesions are most common, albuminuria may be slight and occasionally even absent. There is thus no necessary connection between proteinuria and retinal lesions in Bright's disease.

2. The lesions in the retina are not inflammatory in nature but result from circulatory or metabolic disturbances. The use of the word retinitis is therefore objectionable.

The available evidence indicates that the retinal lesions formerly included in the concept of "albuminuric retinitis" groups together three pathogenetically distinct types of retinopathy. These will be designated in accord with the essential factor in their pathogenesis:

1. *Hypertensive Retinopathy.*—The classical picture of "albuminuric retinitis" occurs only in the presence of hypertension. It will be seen in the following that hypertension is the essential factor in the pathogenesis of the retinal changes.

2. *Arteriosclerotic Retinopathy.*—In chronic Bright's disease there occur retinal lesions which result from retinal arteriosclerosis. While hypertension is most often present in these cases, the same lesions may result from arteriosclerosis in the absence of elevated blood pressure.

3. *Diabetic Retinopathy.*—There is a form of retinal change specifically due to diabetes. Because this retinal change is often associated with

to demonstrate retinal lesions (hypertensive retinopathy and arteriosclerotic retinopathy) in 25 of 32 cases. Hypertensive retinopathy has been present in almost every instance of the malignant phase of essential hypertension that I have observed (see p 827). In chronic cases the different statistics as to the frequency of retinal lesions are in fairly good accord, for here the process usually reaches an advanced stage with typical ophthalmoscopic findings. In acute glomerulonephritis, however, hypertensive retinopathy often does not progress beyond a few initial changes so that the figures given by various authors vary greatly depending on the criteria used. Thus in cases of war nephritis Hinssen and Knack[9] report 9.2 per cent and Hornicker[1] more than 50 per cent. My experience has been that if one studies the eye-grounds carefully and repeatedly a very considerable proportion of the severe cases of acute glomerulonephritis seen on general medical wards show at least such slight abnormalities as clouding of the margins of the disk or narrowing of the arteries. But the proportion of cases of acute glomerulonephritis that develops the typical picture of hypertensive retinopathy is small. I am not aware of any comprehensive investigation on the frequency of retinal changes in patients with postscarlatinal glomerulonephritis.

Hypertensive retinopathy may occur in the acute hypertensive toxemia of pregnancy and eclampsia gravidarum. Hypertensive retinopathy in pregnant women is apt to be extremely severe and rapidly progressive with more tendency to retinal detachment than in other forms. The retinal lesions of the toxemia of pregnancy are discussed further in Chapter 32.

Hypertensive retinopathy occurs at all times of life above early childhood, the incidence corresponding to the frequency of nephritis and the malignant phase of essential hypertension. The youngest case reported seems to be one observed by Bull, a girl aged five years.

The experimental production of hypertensive retinopathy is discussed below (p 376).

Ophthalmoscopic Findings in Hypertensive Retinopathy.—The fully developed picture of hypertensive retinopathy includes changes in the papilla, the retina and the vessels in addition choroidal alterations always present anatomically can often be detected during life. The combination of all these changes results in a most variegated and usually exceedingly characteristic picture which can often be identified with high probability at the first glance through the ophthalmoscope. However in the early stages the appearance of the fundus is not always so characteristic and it is often impossible to say without further observation whether or not the lesion is developing. We shall first consider individually the findings in each of the above mentioned structures.

The Papilla.—Apart from the antecedent contraction of the arteries swelling of the nerve head is the first change to be observed in a high proportion of cases. In the remaining instances in which retinal lesions antedate the papilledema the latter is generally not long in making its appearance. Exceptionally however especially in glomerulonephritis the retinal lesions may be extensive for months or rarely even years before the disk becomes edematous or the patient may succumb without obvious changes in the papilla. The disk is swollen, has indistinct margins and is

Narrowing of the retinal arterioles in acute glomerular nephritis or the toxemia of pregnancy is doubtless due to increased tone. The same is probably true of uniform narrowing unaccompanied by other changes in essential hypertension.

The signs of retinal arteriosclerosis are described in conjunction with arteriosclerotic retinopathy (p. 382).

I. HYPERTENSIVE RETINOPATHY

These retinal lesions are so called because they occur only in the presence of hypertension, are more apt to develop the higher the diastolic pressure and tend to improve or disappear if the blood pressure falls either spontaneously or as a result of treatment. Such disappearance of the retinal lesions after fall in pressure occurs especially dramatically after successful sympathectomy or removal of a suprarenal tumor.

Occurrence.—Hypertensive retinopathy occurs in those forms of Bright's disease which are marked by arterial hypertension. It is therefore not found in focal nephritis, chronic nephrosis or amyloidosis apart from exceptional instances of amyloid contracted kidney with hypertension. Retinal lesions have been described in rare cases of mechanical urinary obstruction (Nettleship,[9] Leber[10]). The hypertension of chronic pyelonephritis may lead to retinal lesions, as may that of periarteritis nodosa. Hypertensive retinopathy may occur in acute lead poisoning without any evidence of renal disease (Oliver,[11] deSchweinitz[12]) as well as in chronic renal disease of plumbic etiology. Oppenheimer and the writer[13] observed hypertensive retinopathy in a patient with hypertension due to a tumor of the suprarenal cortex but practically no changes in the kidney, and many similar cases have since been described. Retinopathy may also accompany the hypertension of pheochromocytoma (Rodin[19]).

The classical picture of hypertensive retinopathy is most commonly seen in the malignant phase of essential hypertension, glomerulonephritis and the hypertensive toxemia of pregnancy. Most larger statistics of the incidence of hypertensive retinal lesions are of older date and limited value because they do not differentiate adequately the individual forms of either the hypertensive disease or the retinal lesion. They show in general that retinal lesions are present in from 20 to 35 per cent of patients dying with contracted kidneys. Thus Miley[14] found retinal changes in 32.6 per cent of 156 such cases, Widal and Weill[15] in 32 per cent of 166 cases, and Groenouw[16] in 22.4 per cent of 935 cases of Bright's disease reported by various authors, the large majority of which were chronic forms, *i. e.*, chronic glomerulonephritis and essential hypertension. Fishberg and Oppenheimer[17] observed hypertensive retinopathy in 17 of 55 cases of chronic glomerulonephritis and in 37 of 189 cases of essential hypertension. The material studied by the last named authors consisted in hospital patients; in private or dispensary practice the incidence of retinal lesions is not nearly so high. However, these statements hold for patients seen only for a short period; by following patients with chronic glomerulonephritis for periods up to fourteen years, Cannady and O'Hare[18] were able

A most prominent feature in most cases is the appearance in the retina of white spots composed of areas of fatty change and edema. They are usually confined to the portion of the retina within 3 or 4 disk diameters from the papilla. At the start they frequently present an appearance characterized by the terms "cotton wool" or "snow bank" areas. Later, if not absorbed, they become more and more sharply outlined, bright white and shiny, or yellowish and densely opaque, thus resembling the type of spots that predominate in arteriosclerotic retinopathy. The change is apparently largely due to absorption of edema. Sometimes these sharply defined "hard" spots are present from the onset. The white areas are often rounded but may be irregular in outline, and are occasionally surrounded by hemorrhage; they vary from tiny to very large in size. The fatty degeneration usually occurs deep in the retina so that the larger vessels pass over it, but the reverse is exceptionally true. Most often the white areas are in the proximity of the larger vessels. The large white areas may become confluent with one another and by joining with the white zone around the papilla described in the preceding paragraph, convert the central portion of the retina into an extensive dense white area extending several disk diameters from the papilla.

The larger white lesions usually spare the macula. In this region there often appear small white "hard" spots, usually in a linear arrangement radiating from the fovea centralis and making up the well known stellate figure. But it is to be emphasized that the stellate figure does not appear in by any means all cases, and when present it is usually a late phenomenon. The stellate figure also is seen in some cases of arteriosclerotic retinopathy. The reason why the fine white spots assume the stellate arrangement around the macula is not definitely known. Dimmer[3] believes the cause lies in the anatomical arrangement of the external fiber layer in which the lesions are located.

Hemorrhages are commonly present from an early stage; at times they represent the first discernible change in the retina. Often they are flame shaped. Others are elongated or linear extravasations, the long diameter mostly radial to the disk. They are frequently parallel and close to a large vessel. Sometimes the hemorrhages seem to be into the perivascular sheath. Rounded or irregular hemorrhagic spots are more common peripherally. In the later stages the hemorrhages usually diminish in number, the picture being dominated by the white spots. Not very rarely no hemorrhages at all are to be seen. Great predominance of hemorrhages in one eye should raise the suspicion of closure of a central vessel.

In cases of long standing, pigmented areas arising from proliferation of the pigment epithelium may be seen, particularly in the periphery. But they are generally not nearly as prominent ophthalmoscopically as anatomically.

The Vessels. – The arterial blood columns are narrowed, often to a very great extent. Sometimes the constriction is so marked that there appear to be fewer arteries present than the normal number and they cannot be followed the usual distance out from the disk. The reflex stripe of the narrowed arteries is often very bright, resulting in the appearance termed "silver wire arteries" by Gunn.[4] As mentioned above, Gowers[5] observed

most often reddened although the hyperemia is rarely of high degree. The swelling of the nerve head is largely due to edema, in addition to venous hyperemia, giving it a cloudy appearance. The papilledema is nearly always accompanied by a similar swelling of the adjacent parts of the retina so that the margins of the disk become indistinct and it may be impossible to make out the delimitation of the papilla from the surrounding retina. In other exceptional cases, on the contrary, the swelling of the disk causes it to rise abruptly from the retina so that the appearance is very similar to that of choked disk resulting from tumor of the brain. Keith, Wagener and Kernohan[1] have observed swelling of the disk of as much as 6 diopters in the malignant phase of essential hypertension and 3 or 4 diopters is not very rare. In most instances the absence of abrupt transition resulting from the peripapillary edema makes the estimation of the elevation of the disk difficult or impossible. With the use of the Gullstrand ophthalmoscope Larsson[2] demonstrated elevation of the disk in all his cases of hypertensive retinopathy.

As a rule the disk is not only swollen but also more or less reddened. The reddening is evidently dependent on venous hyperemia, for the veins are usually dilated and the arteries narrow. The color of the disk is greatly influenced by the hemoglobin content of the blood; if the patient is markedly anemic, which is more often the case in chronic glomerulonephritis than in the malignant phase of essential hypertension, the disk may be very pale. Very often both the hyperemia and the swelling of the disk diminish in the course of a long standing process. In glomerulonephritis papilledema may improve greatly or in rare instances disappear entirely while the retinal changes remain or even progress; in such cases there may be more or less atrophy of the nerve head.

Choked Disk Associated with Edema of the Brain.—In some instances of glomerulonephritis, the hypertensive toxemia of pregnancy and the malignant phase of essential hypertension, edema of the brain leads to very marked increase in intracranial pressure (cerebrospinal fluid pressure over 400 mm. of water). The heightened intracranial pressure is associated with swelling of the disk appearing like the choked disk of brain tumor. Most often the papilledema is accompanied by other evidences of hypertensive retinopathy. But exceptionally, especially in acute glomerulonephritis in children, the choked disk is not associated with retinal changes. In these rare cases it seems likely that the papilledema results from the increased intracranial tension, and it has been observed to clear up after decompression.

The Retina.—The papilledema may be present for a considerable time before changes in the retina appear. In other cases retinal lesions appear very early and may precede the papilledema.

At an early stage there often appears a grayish clouding of the retina best marked close to the papilla and diminishing toward the periphery. This is largely due to edema, but there is also some ganglioform swelling of the nerve fibers. If the process progresses, the grayish cloudy hue of the retina around the disk becomes more and more white and opaque. Finally by confluence with the white spots in the retina about to be described there may arise a dense white area completely surrounding the disk.

long ago that narrowing of the arteries is the first change in the eye-ground in hypertensive retinopathy But there may be marked narrowing of the retinal arteries in hypertensive patients for many years without any retinal lesions developing

When hypertensive retinopathy develops in an individual who has had hypertension for a considerable period evidence of retinal arteriosclerosis is usually also present In such cases, of course arteriosclerotic changes in the retina may be combined with hypertensive retinopathy

The veins are generally dilated which in combination with the narrowed arteries results in an abnormally great disproportion between the two varieties of vessel Arterio-venous compression may be very plain

Types of Hypertensive Retinopathy —In the preceding paragraphs the changes in the individual structures of the fundus oculi which may enter into the picture of hypertensive retinopathy have been described The lesions vary in prominence in different instances with resultant variations in the composite ophthalmoscopic picture Thus in some cases, papilledema is the only change in the fundus apart from narrowed arteries In fact Moore[27] observed a patient in whom the papilledema was unilateral I have repeatedly observed the papilledema to be unilateral for weeks In other instances the papilledema is but slight for a considerable period while the retinal lesions are marked of the latter either hemorrhages or white areas of degeneration and edema may overwhelmingly predominate

As a result of their extensive studies Keith Wagener and Kernohan[4] believe that they can often differentiate the ophthalmoscopic picture of hypertensive retinopathy in the malignant phase of essential hypertension from that occurring in glomerulonephritis According to these investigators In malignant hypertension the edema of the retina is less extensive and less dense and there is little tendency to the formation of peripapillary snow bank exudates Edematous detachment of the retina was seen in only one case in the present series The hyperemia of the disk is in marked contrast to the anemia of the disk and the retina that is seen in the retinitis of nephritis Sclerosis of the retinal arterioles is always present in malignant hypertension and is usually absent in chronic nephritis However while these associations hold in most cases there are also many instances in which such ophthalmoscopic differentiation between the malignant phase of essential hypertension and glomerulonephritis is impossible It is to be remembered that in chronic glomerulonephritis of many years duration sclerosis of the retinal arteries may be very marked while on the other hand sclerosis of the retinal arteries may not be recognizable with the ophthalmoscope in the malignant phase of essential hypertension in very young subjects The color of the disk and retina is greatly influenced by the hemoglobin content of the blood which would appear to be one reason why these structures are generally more pale in glomerulonephritis than in essential hypertension

Hypertensive retinopathy appears to be of the same pathogenesis (see below) in both essential hypertension and glomerulonephritis the difference in ophthalmoscopic appearance if present being largely the result of the concomitant operation of other factors

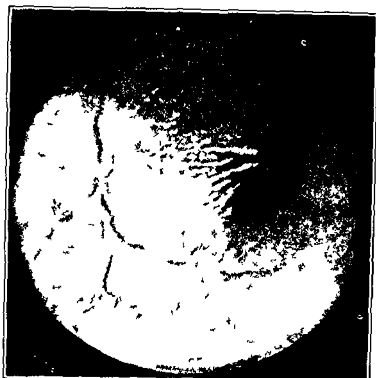


FIG 6 —Hypertensive retinopathy in chronic glomerulonephritis (Courtesy of the late Dr Robert K Lambert The double white disk temporal to the papilla in the photograph is an artefact)

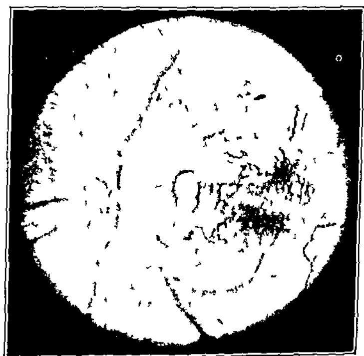


FIG 7 —Hypertensive retinopathy in the malignant phase of essential hypertension (Courtesy of the late Dr Robert K Lambert)

long ago that narrowing of the arteries is the first change in the eye-ground in hypertensive retinopathy. But there may be marked narrowing of the retinal arteries in hypertensive patients for many years without any retinal lesions developing.

When hypertensive retinopathy develops in an individual who has had hypertension for a considerable period, evidence of retinal arteriosclerosis is usually also present. In such cases, of course, arteriosclerotic changes in the retina may be combined with hypertensive retinopathy.

The veins are generally dilated, which in combination with the narrowed arteries results in an abnormally great disproportion between the two varieties of vessel. Arterio-venous compression may be very plain.

Types of Hypertensive Retinopathy.—In the preceding paragraphs the changes in the individual structures of the fundus oculi which may enter into the picture of hypertensive retinopathy have been described. The lesions vary in prominence in different instances with resultant variations in the composite ophthalmoscopic picture. Thus, in some cases, papilledema is the only change in the fundus apart from narrowed arteries. In fact, Moore[7] observed a patient in whom the papilledema was unilateral. I have repeatedly observed the papilledema to be unilateral for weeks. In other instances the papilledema is but slight for a considerable period while the retinal lesions are marked; of the latter, either hemorrhages or white areas of degeneration and edema may overwhelmingly predominate.

As a result of their extensive studies, Keith, Wagener and Kernohan[3] believe that they can often differentiate the ophthalmoscopic picture of hypertensive retinopathy in the malignant phase of essential hypertension from that occurring in glomerulonephritis. According to these investigators, "In malignant hypertension the edema of the retina is less extensive and less dense and there is little tendency to the formation of peripapillary snow bank exudates. Edematous detachment of the retina was seen in only one case in the present series. The hyperemia of the disk is in marked contrast to the anemia of the disk and the retina that is seen in the retinitis of nephritis. Sclerosis of the retinal arterioles is always present in malignant hypertension and is usually absent in chronic nephritis."

However, while these associations hold in most cases, there are also many instances in which such ophthalmoscopic differentiation between the malignant phase of essential hypertension and glomerulonephritis is impossible. It is to be remembered that in chronic glomerulonephritis of many years duration sclerosis of the retinal arteries may be very marked, while on the other hand sclerosis of the retinal arteries may not be recognizable with the ophthalmoscope in the malignant phase of essential hypertension in very young subjects. The color of the disk and retina is greatly influenced by the hemoglobin content of the blood, which would appear to be one reason why these structures are generally more pale in glomerulonephritis than in essential hypertension.

Hypertensive retinopathy appears to be of the same pathogenesis (see below) in both essential hypertension and glomerulonephritis, the differences in ophthalmoscopic appearance, if present, being largely the result of the concomitant operation of other factors.

Pathological Anatomy of Hypertensive Retinopathy.—The anatomical basis of hypertensive retinopathy was exhaustively studied by Leber,[10] whose masterly description I here largely follow. More recent anatomical studies have been published by Wagener,[8] Keith, Wagener and Kernohan,[2] Friedenwald[29] and Manlove.[30]

The retinal changes are almost altogether confined to a zone of from 5 to 6 mm. from the papilla, being absent or slight beyond this. In acute cases there is usually edematous transudation into the papilla and the neighboring retinal tissue. This may be so copious as to produce large spaces filled with fluid between the tissue elements. The form of the hemorrhages has been described above; the radially elongated ones are situated in the nerve fiber layer. The extravasation is, according to Leber, largely by diapedesis.

The white spots ("exudates") are for the most part made up of large cells laden with fat and lipoid, so-called fat granular cells. They contain particularly large amounts of cholesterol esters exhibiting double refraction through the polarizing microscope. Swelling and necrosis of these cells leads to the formation of the so-called "cytoid bodies," which are often prominent in the sections. In the early phases, edema may be prominent between the retinal elements. Another factor in the formation of the more superficial white spots is a ganglioform swelling of the nerve fibers. Fatty changes also occur in the glia fibers. The origin of the fat granular cells is disputed. Leber believes that they are derived from the pigment epithelium, others from glia cells, and the opinion has also been advanced that they are leukocytes. It seems certain that they take up the fat locally, but from what elements this comes is unknown. It is surprising how well the retinal elements may be preserved for a long time in the midst of fatty areas, but ultimately there is great destruction of the granular layers, the rods and cones, and other elements. According to Friedenwald the great majority of the lesions which have the ophthalmoscopic appearance of "cotton wool exudates" have gone on to the stage of focal necrosis. When the white spots disappear, which they often do, Leber believes this occurs largely through removal of the fat granular and necrotic cells *via* the blood vessels.

Leukocytic and lymphocytic infiltration is almost always minimal or absent; when white blood cells are present they are largely perivascular. The pigment epithelium proliferates in some places and disappears in others.

The arterioles show lesions in at least the large majority of instances. These arteriolar changes are of various types—hyalinization, fatty changes, necrosis, endothelial proliferation and muscular hypertrophy and other alterations in the media. They have been studied in detail by Friedenwald,[29] to whose work the reader is referred. According to this investigator the primary change is an acute necrosis of the vessel wall, the outcome of which may be hyalinization and lipoidosis. Friedenwald found that the lesion is located primarily in the precapillary arterioles, but also often affects the capillaries and sometimes the larger vessels. In Manlove's[30] observations the most common arteriolar lesions were medial hypertrophy and intimal proliferation; hyalinization of part or all the arteriolar wall was seen frequently and necrosis rarely. These changes were more pronounced

in the choroid than in the retina. By measuring the wall lumen ratio Manlove demonstrated thickening of the walls of the retinal arterioles in malignant hypertension. The severity of the arteriolar changes varies greatly from case to case. Friedenwald found them in all his cases. However Schieck[31] and others long ago published observations in which arteriolar lesions were minimal or absent. Manlove studied several instances of malignant hypertension with numerous exudates and hemorrhages in which there was no arteriolar disease except a little medial thickening. In hypertensive retinopathy in the malignant phase of essential hypertension Keith, Wagener and Kernohan found the obstruction greater in the arterioles of the choroid than in those of the retina.

Lesions in the choroid are almost always to be found in the form of leukocytic infiltrations, edematous transudates and arteriolar thickening.

The Pathogenesis of Hypertensive Retinopathy.—From the first description of retinal lesions in *renal disease* their origin has been ascribed to abnormalities in the composition of the blood resulting from deficient function of the kidney. Widal, Morax and Weill[32] found that the retinal changes occur only in those varieties of renal disease which are associated with nitrogen retention; all 17 of their patients with hypertensive retinopathy had increased urea content of the blood. They therefore believed that the retinal changes are the result of *nitrogen retention*, a view which was formerly widely accepted. But as a matter of fact many patients with typical hypertensive retinopathy have intact renal function *and no nitrogen retention*; a series of such cases was published by Wagener and Keith[33] and they are to be seen frequently on an active medical service. Not very rarely hypertensive disease runs a protracted course with severe retinal changes to terminate finally in death without there having been at any time nitrogen retention. On the other hand many patients die of uremia with great nitrogen retention but no retinal lesions. From these facts it seems clear that renal excretory insufficiency is not the essential cause of hypertensive retinopathy.

Because of the presence of large quantities of cholesterol esters in the white spots of hypertensive retinopathy and the frequency of hypercholesteremia in certain varieties of renal disease, Chauffard[34] believed the *increased cholesterol content of the blood* to be the cause of white spots in the retina, the other changes having a different pathogenesis. This theory was quite generally held in France. But it seems untenable, for in the very form of renal disease in which hypercholesteremia is most marked, chronic nephrosis, the retinal lesions do not occur. On the other hand, in the end stages of chronic glomerulonephritis and essential hypertension, in which the retinal changes are most common, the cholesterol content of the blood is rarely notably elevated and is in fact often subnormal if nitrogen retention is present. When present, however, increased lipid content of the plasma may well secondarily favor the deposition of lipids in the retinal lesions.

Another view that must be abandoned is that hypertensive retinopathy results from *arteriosclerotic narrowing of the arteries of the retina* (von Michel[35] and others). While marked intimal thickening is present in many instances of hypertensive retinopathy, in others the vessels present

no considerable changes of other than recent origin Moreover, extensive retinal lesions may supervene so rapidly in cases of acute glomerulonephritis and eclampsia gravidarum that it seems very improbable particularly in children, that sclerotic changes could develop in so short a time Arteriosclerosis does, of course, produce retinal lesions but these differ from the manifestations of hypertensive retinopathy and will be described in the next section But that *acute* arteriolar lesions not included in the conventional conception of arteriosclerosis, may play a part in producing the retinal lesions, will be seen below

The one fact fundamental to any adequate consideration of the pathogenesis of hypertensive retinopathy is that it always occurs in association with *arterial hypertension* as was long ago realized by Traube[36] on the basis of palpation of the pulse and observation of cardiac hypertrophy, and more recently emphasized and elaborated by Volhard[37] In almost every patient with hypertensive retinopathy the blood pressure is high in the few in whom this is not the case, the pressure has dropped because of cardiac weakness or the process is regressing Moreover the hypertension precedes the retinal changes In glomerulonephritis retinal changes develop only after the blood pressure has risen and the retinal lesions heal if the hypertension disappears Likewise in the toxemia of pregnancy retinopathy develops only in the wake of hypertension and clears up when the blood pressure falls In essential hypertension the retinal lesions under discussion appear only in those cases with very high blood pressure If low sodium diet the use of hypotensive drugs sympathectomy or ablation of a suprarenal tumor removes hypertension the retinal lesions clear up Clinical evidence thus leaves no doubt that the retinal lesions are consequences of hypertension or of the processes which produce hypertension

That hypertension can produce retinal lesions was shown by Keyes and Goldblatt[38] in dogs and monkeys with constricted renal arteries Similar observations were made by Fasciolo and Cramer[39] and Laughlin *et al*[40] When chronic hypertension lasting years was produced by clamping of moderate degree there developed tortuosity increased light reflex and white sheathing of the arterial blood columns Hemorrhages cotton wool exudates edema of the retina and papilledema developed in the more pronounced cases Like the retinal lesions of human hypertension this retinopathy was not due to renal insufficiency for it appeared in the absence of nitrogen retention Histologically the retinal arterioles revealed hyalinization endothelial hyperplasia and medial hypertrophy When the clamp was tightened enough to produce malignant hypertension with very high blood pressure and widespread arteriolar necrosis the retinal arterioles also became necrotic The fundus then was the seat of lesions more severe than those seen in human hypertension—extensive hemorrhages retinal and subretinal edema detachment—and there was bleeding into the anterior and posterior chambers of the eye

The question then arises of the mechanism through which hypertension produces the retinal lesions It would seem that four factors may be involved

1 Constriction of the retinal arterioles
2 Increased capillary pressure in the retina

3 Lesions of the retinal arterioles
4 Increased intracranial pressure

1 *Constriction of the Retinal Arterioles* —Volhard has advanced the theory that the retinal lesions are the result of *angiospastic ischemia of the retina* the retinal *arterioles* being involved in the general vasoconstriction that produces the hypertension

In hypertensive retinopathy as mentioned above the retinal arteries are narrowed often to an extreme degree Gowers[3] knew long ago that the narrowing of the retinal arteries may be present at a very early stage I have observed marked narrowing of the arteries of the retina in acute *glomerulonephritis* as long as two weeks before lesions of the retina appeared Well in accord with Volhard s theory are the sometimes strikingly sudden and early appearance of retinal lesions in acute glomerulonephritis and the regression of the retinal changes if the renal process heals In this connection it seems significant that retinal changes identical both ophthalmoscopically and histologically with those of hypertensive retinopathy are occasionally observed in cases in which the retinal circulation has been hampered by increased intracranial tension in brain tumor Furthermore the typical stellate figure around the macula has been noted in various forms of anemia with regression after the hemoglobin has risen (de-Schweinitz[41] Augsten[42]) That spasms of the retinal arteries have been actually observed during hypertensive paroxysms was mentioned on page 3?2

Very important support has been afforded to Volhard s angiospastic theory of hypertensive retinopathy by the beautiful observations of Haselhorst and Mylius[43] They observed ophthalmoscopically spasms of the retinal arteries in a woman with eclampsia gravidarum At the first examination they found the eye ground completely normal except for cramp-like contractions of longer and shorter stretches of the arteries The location of these constrictions changed rapidly and they were able to see the previously narrowed segment of the vessel fill again with blood as the spasm relaxed By two days later the spasms had become more constant and involved longer stretches of the arteries At this time the first changes in the retina appeared which consisted at first of circumscribed indistinctly limited transparent glassy whitish yellow lesions appearing initially midway between the larger arterial branches Soon however they were visible scattered irregularly over the entire posterior pole Besides these there also arose a fairly diffuse edema of the macular region Vision became so badly impaired that at times fingers could not be distinguished Cesarian section was performed and the patient rapidly improved The vessels gradually filled vision returned and the retinal changes regressed though six months later some cholesterol crystals were still present in the macula Haselhorst and Mylius photographed each stage of the retinal process and reproduced a number of convincing photographs

2 *Increase in Retinal Capillary Pressure* —In the foregoing it has been seen that there is strong evidence that angiospastic ischemia of the retina is concerned in the pathogenesis of hypertensive retinopathy It seems probable however that the reverse process increase in retinal capillary pressure may also be concerned This conception was suggested by the

observation that in many patients who had undergone thoracolumbar sympathectomy for essential hypertension, *papilledema, hemorrhages and exudates cleared up pari passu with fall in arterial pressure despite persistence of constriction of the retinal arteries, as evinced by attenuated arterial blood columns* Such clearing of retinopathy in the presence of lower arterial pressure and persistent retinal arterial constriction does not harmonize with an ischemic pathogenesis of the lesions but points rather to causation of the latter by increased capillary pressure That capillary hypertension could produce hemorrhages and edema is evident And the underlying basis of many so-called exudates is transudation of plasma from which fluid is then abstracted, leaving lipo protein deposits

A working hypothesis of the pathogenesis and role of increased capillary pressure in hypertensive retinopathy is the following In the case of the brain it has been proved (p 302) by the finding of normal cerebral blood flow that the rise in arterial pressure is accompanied by commensurate increase in cerebral vascular resistance due to constriction of the cerebral arterioles While retinal blood flow has not been measured the narrowing of the arterial blood columns indicates that the retinal arteries are similarly constricted in hypertension But like the cerebral arterioles the retinal arterioles have only a thin muscular coat* and therefore doubtless share with the cerebral arterioles a much less powerful vasoconstricting ability than the arterioles of the extremities (p 354) When the arterial pressure rises sufficiently the arterioles of the retina may not be able to constrict with sufficient strength to maintain the homeostasis of the retinal circulation The consequence would be rise in hydrostatic pressure in the retinal capillaries with resultant edema (papilledema, exudates) and hemorrhages This hypothesis attributes to hypertensive retinopathy a pathogenesis akin to that of cerebral edema in hypertensive encephalopathy But that it is no more than a working hypothesis is to be reiterated

3 *Lesions of the Retinal Arterioles* —It was mentioned above that necrotizing and other acutely developing regressive arteriolar lesions occur in some percentage of instances of hypertensive retinopathy Friedenwald [9] found that these arteriolar lesions are definitely related to the focal lesions hemorrhages and so-called exudates characteristic of albuminuric retinitis Acute damage to the arteriolar walls (we are not here considering gradually developing arteriolar sclerosis), when it occurs is thus one of the intermediaries through which hypertension produces retinal changes But the arteriolar necrosis and marked initimal proliferation in question are present in only some of the cases and are probably only a minor factor in at least most of the others In malignant hypertension Manlove[30] was unable to demonstrate that arteriolar changes result in other retinal lesions and observed cases with many hemorrhages and exudates in the absence of arteriolar disease

* Manlove s[30] measurments show that the walls of the retinal arterioles are thinner in relation to the lumen than those of even the brain and of all organs studied except the lungs He quotes Coats as having also found that the walls of arterioles observed in the eye are thinner than those in other organs

4 *Increased Intracranial Pressure*—In recent years it has become clear that increased intracranial pressure due to edema of the brain plays an important role in the pathogenesis of a high proportion of instances of hypertensive retinopathy. This was long ago stated by Cushing and Bordley[44] who observed disappearance of the retinal lesions following reduction of intracranial pressure by subtemporal decompression. Similar observations have been made by Puech and Thiery[45] and others. Larsson[46] found the pressure of the cerebrospinal fluid elevated in hypertensive patients with papilledema. Shelburne, Blain and O'Hare[48] observed that 19 of 20 hypertensive patients with a cerebrospinal fluid pressure of over 200 mm. of water had papilledema, while the latter was present in only 2 of 30 with lower tension of the liquor. Pickering[47] found hypertensive retinopathy in all his hypertensive patients with cerebrospinal fluid pressure over 250 mm. of water; this lesion was present in only 1 of 21 patients with lower cerebrospinal tension (and even in this exception the tension may have been secondarily lowered by dehydration due to vomiting). The writer has also found the cerebrospinal pressure elevated, though sometimes but slightly, in all instances of hypertensive retinopathy in which papilledema was well marked and often also when it was but slight. But I have repeatedly observed normal pressure of the cerebrospinal fluid in hypertensive retinopathy at a time when there was little or no edema of the disk, even though the retinal lesions were very severe. Well marked papilledema in hypertensive retinopathy is evidently correlated with increased intracranial pressure. The same is true of pronounced distention of the retinal veins, which often precedes manifest edema of the disk.

It would thus appear that hypertensive retinopathy is a consequence of circulatory disturbance in the retina. The homeostasis of the retinal circulation demands that the arteriolar resistance, i.e., the caliber of the arterioles, be altered commensurate with the rise in systemic arterial pressure in order that the all important capillary pressure and flow remain unchanged. Hypertensive retinopathy would appear to result from disturbances in this circulatory homeostasis. Hypertension engenders these circulatory disturbances through the intermediacy of four mechanisms—constriction of the retinal arterioles, increase in retinal capillary pressure, lesions of the walls of the retinal arterioles, and increased intracranial pressure. The relative importance of these factors varies in different instances of hypertensive retinopathy and thereby accounts in large part for the diversity of the ophthalmoscopic pictures. Where papilledema and venous distention are pronounced, increased intracranial pressure is present. The importance of the factor of retinal arteriolar constriction can presumably be evaluated by the caliber of the arteriolar blood columns. Very thin arteriolar blood columns, especially when the attenuation evolves under observation, speaks for constriction. Clearing of the lesions when the arterial tension falls (e.g., after sympathectomy) despite persistence of the arterial narrowing speaks for the operation of raised retinal capillary pressure. Regarding the ophthalmoscopic manifestations of the acute arteriolar lesions here under discussion (we are not considering long standing arteriolar sclerosis) little is known. According to Wilmer

Pierce and Friedenwald,[48] hyaline thickening and necrosis are manifested by a copper wire appearance of the vessels That accompaniment of the causative hypertension by hypoproteinemia or hypercholesterolemia would influence the form of the retinal lesions seems plausible

The Symptoms of Hypertensive Retinopathy —In rare instances, impairment of vision due to hypertensive retinopathy is the first symptom of hypertensive disease, the patient going to an ophthalmologist in the belief he needs glasses Such cases occur particularly in the malignant phase of essential hypertension More often, patients with very extensive changes in the retina make no complaint about disturbances of vision this is because the macula is relatively unaffected In other cases, there are varying degrees of impairment of vision, attaining in unusual instances a high degree of amblyopia Complete blindness as a result of hypertensive retinopathy is extremely rare it may be due to hypertensive encephalopathy, which may be proved by complete recovery of vision within a short time without any improvement in the objective retinal findings There is usually no considerable narrowing of the visual fields Color scotomata particularly circumscribed areas of blue blindness have been reported in many cases

Complications of Hypertensive Retinopathy —Of these the most important is detachment of the retina, in 204 cases collected from the literature by Leber it occurred in 2 9 per cent Detachment of the retina is decidedly less rare in hypertensive retinopathy during pregnancy than in other cases It is usually bilateral The prognostic significance of detachment of the retina is very bad in all cases except those occurring during pregnancy the duration of life being short (Leber[10]) If termination of pregnancy halts the basic disease the retina re-attaches with healing The same occurs in very rare cases apart from those during pregnancy Moore[27] mentions one such case in which the man lived for seven years after the detachment and I saw a young woman with chronic glomerulonephritis who was alive a year and a half after detachment of the retina resulting from hypertensive retinopathy

Other rare complications are closure of the central artery or vein or their branches secondary glaucoma and hemorrhage into various portions of the eyeball These are probably almost always due to concomitant arteriosclerosis Another rare complication is sudden blindness due to hypertensive encephalopathy

Prognostic Significance of Hypertensive Retinopathy —The appearance of hypertensive retinopathy has long passed and rightly so as a very ominous prognostic sign This is particularly the case in chronic glomerulonephritis and essential hypertension in which the appearance of hypertensive retinopathy is one of the strongest evidences that the disease has entered on its last phase Numerous statistics have shown that about 90 per cent of patients with hypertensive retinopathy die within two years Most of the few that survive the first two years die within the next year or two Individual cases have been recorded that survived long periods Leber[10] mentions one that is said to have lasted seventeen years I observed a hypertensive patient who had typical hypertensive retinopathy that cleared up after about a year despite persistence of his hypertension he

was able to work for nine years His condition then became worse and the retinal lesion reappeared Necropsy disclosed the typical findings of the malignant phase of essential hypertension Keith and Wagener[49] report 15 cases in which the papilledema of malignant hypertension receded without specific therapy

In essential hypertension sympathectomy may be followed by rapid and complete clearing of hypertensive retinopathy, which may or may not recur The same may follow rigid salt restriction or the successful use of anti hypertensive drug The disappearance of hypertensive retinopathy following successful removal of cortical or medullary adrenal tumors has been mentioned it has also been observed when hypertension has been relieved by unilateral nephrectomy (Kennedy[50] et al Roberts[51])

In acute glomerulonephritis while the presence of typical hypertensive retinopathy indicates that the disease is severe the outlook is not nearly as bad as in chronic states and some patients recover despite the presence of marked retinal changes Indeed if one examines the eye grounds repeatedly retinal changes of slight degree notably one or a few hemorrhages are to be found in many cases that have a mild course Well marked retinal lesions can heal—though this is exceptional—either with complete *restitutio ad integrum* of the retina or leaving behind the residua described below Thus the appearance of hypertensive retinopathy in acute glomerulonephritis does not mean an unconditionally bad prognosis

The ultimate outcome of retinal changes occurring with hypertensive disease in pregnancy and eclampsia gravidarum generally hangs together with that of the hypertension and renal process If termination of pregnancy is followed by healing of the kidneys and fall in blood pressure the retinal process will also regress The healing of the retinal lesions may be complete or a permanent defect of vision may remain This may be slight or severe in unusual instances almost complete blindness results Detachment of the retina is usually completely repaired if the patient survives The appearance of hypertensive retinopathy during pregnancy is evidence of a severe and rapidly progressive process and is an indication for termination of pregnancy Almost all toxemic patients with hypertensive retinopathy remain with permanent hypertension (*cf* p 962)

Spontaneous Healing – When hypertensive retinopathy is followed over a considerable time evidences of healing in the form of absorption of individual exudates and hemorrhages and diminution in papilledema are usually observed As a rule these are more than counterbalanced by fresh lesions that appear But if the fundamental disease acute glomerulonephritis or hypertensive disease in pregnancy regresses accompanying hypertensive retinopathy will also clear up Under such circumstances very severe retinal processes may disappear completely though this is of course rare In these rare cases the stellate figure around the macula composed of fine sharply delimited spots is usually the last to clear up The fundus may thus return to normal or more often if the process has been well marked changes are left The disk is atrophic appearing white and very sharply delimited The arteries may be narrowed with white lines accompanying them Holm[52] and others have described cases in which there was extensive circumpapillary formation of connective tissue with jagged outlines as an indication of shrinkage

There may, on very rare occasions, be a recurrence of fresh changes in a retina which is the seat of a healed process dating from a previous attack of glomerulonephritis or hypertensive disease in pregnancy. Such a case was observed in a boy, aged thirteen years, who remained amaurotic in one eye following the healing of retinal lesions accompanying acute glomerulonephritis four years previously. Both eyes showed evidences of optic atrophy; the arteries were much narrowed with white streaks on either side and in the macular region of the amaurotic left eye there was a dense old white area. The recent changes consisted in hemorrhages and white spots, but there was no notable change in the atrophic papilla. These fresh lesions cleared up, leaving the retina as it had been before the second exacerbation.

II. ARTERIOSCLEROTIC RETINOPATHY

While it has long been known that arteriosclerosis can produce retinal lesions, the more severe retinal manifestations of arteriosclerosis are included in the old literature under the concept of "albuminuric retinitis." So far as I am aware, Foster Moore[53] was the first to give an adequate description of the variegated retinal pictures resulting from arteriosclerosis and to differentiate them from what he termed renal retinitis. He called the condition arteriosclerotic retinitis, but inasmuch as the process is clearly not inflammatory in nature, we shall use the term arteriosclerotic retinopathy.

Retinal arteriosclerosis occurs in individuals who have had high blood pressure for a considerable period, usually many years. O'Hare and Walker[54] pointed out that widespread arteriosclerosis of the large vessels in the absence of hypertension is most often not accompanied by notable changes in the retinal arteries. However, there are exceptional cases in which retinal arteriosclerosis and arteriosclerotic retinopathy develop in the absence of hypertension. As would be expected from its connection with long-standing hypertension, retinal arteriosclerosis is seen most frequently in essential hypertension (p. 813), but is not rare in chronic glomerulonephritis. I have also seen retinal arteriosclerosis in hypertension resulting from amyloid contracted kidneys and from polycystic disease of the kidneys. Diabetic retinopathy may or may not be accompanied by ophthalmoscopically demonstrable arteriosclerosis. Judging by the description given by Duckworth,[55] gouty retinitis, which I have not seen, may be a form of arteriosclerotic retinopathy.

Signs of Retinal Arteriosclerosis.—The ophthalmoscopic manifestations of retinal arteriosclerosis vary considerably in individual cases, for which reason there has not been complete accord as to the relative value of the individual signs. Still not elucidated in all respects is the differentiation of hypertonicity of the retinal arterioles and thickening of their walls. Among the more valuable signs are the following:

1. Irregularity of outline of the arterial blood columns resulting from persistent circumscribed constrictions and dilatations of the lumen of the artery is evidence of well marked arteriosclerosis. It is a common sign but is not definitely demonstrable in all cases. Irregularity of the arterial

lumens is generally observed only in long standing arterial disease but Moore[7] saw it develop to a high degree within eighteen months in a case of war nephritis Leatham[8] observed irregularity of the borders of the arterial blood columns in 76 per cent of his hypertensives So high a percentage will be detected only by careful examination of all the arteries out to the smallest visible branches Seeming irregularities due to the refractive media are eliminated by examination from a little different angle Transient irregularities due to spasm are mentioned above, their detection is rare. Definite irregularity of the arterial lumen hardly occurs in the absence of arterial disease

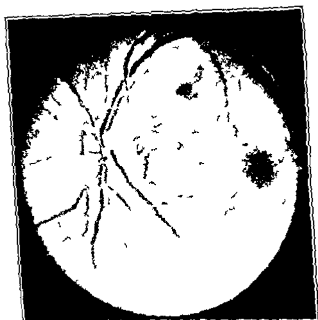


Fig 8 —Retinal arteriosclerosis in essential hypertension, note the arterio-venous compression above (Courtesy of the late Dr Robert K Lambert)

Uniform narrowing of the arterial blood columns is not in itself evidence of arteriosclerosis it may appear with the hypertension of the toxemia of pregnancy or acute glomerulonephritis before there has been time for the development of thickening of the walls Such narrowing is presumably a manifestation of hypertonicity of the muscular coat In the aged narrow retinal arteries are not uncommon despite the absence of any evidence of hypertension past or present Whether this attenuation bespeaks uniform thickening of the arterial wall remains to be established

2 Visibility of the arterial walls is evidence that they are diseased in the visible stretch When the change is well marked the walls are seen as white streaks bordering the arterial blood columns for varying distances

3 Arterio venous compression long ago described by Gunn[9] is often a striking manifestation of retinal arteriosclerosis but it is absent in many

instances When the vessels are healthy, the retinal veins are visible until they reach the arterial blood column under which they pass and often through it If arterio-venous compression is present, the vein becomes invisible or appears attentuated for a short distance from the edge of the arterial blood column under which it passes Shelburne[57] points out that crossings within one disc diameter of the papilla should not be used for evaluation of nicking for here the latter may be simulated by the vein dipping deep into the retina In a good many instances one can observe that the flow of blood in the vein is actually impeded, for the venous blood column is wider and darker before reaching the artery than after Another feature pointed out by Moore is that the vein often bends so as to pass under the vein at approximately a right angle The ophthalmoscopic finding termed arterio-venous compression is probably of diverse causation It has been generally thought that the loss of visibility of the vein for some distance from the arterial blood column is due to opacity of the sclerosed and thickened arterial wall under which the vein passes Another factor that probably also plays a part has been brought out by Friedenwald[9] who has demonstrated that artery and vein are enclosed in a common connective-tissue sheath at the point of crossing which is greatly thickened when arteriosclerosis is present The thickening of the arterial wall and the common connective-tissue sheath causes the appearance of arterio venous compression not only through their opacity but, very likely also through displacing the vein into deeper layers of the retina[7]

Slight degrees of arterio-venous nicking are sometimes seen in health But the well marked phenomenon with a complete gap between the artery and the two ends of the vein occurs only with present or past hypertension of marked degree The finding of pronounced arterio venous compression in a normotensive individual thus permits the inference of antecedent marked hypertension In Shelburne's observations it took years of marked hypertension for the evolution of a high degree of arterio venous nicking

4 Increased tortuosity of the arteries is a frequent manifestation of arteriosclerosis However healthy vessels may also be quite tortuous so this sign must be evaluated with caution unless it is very marked Of particular significance though rare is a 'cork-screw appearance of the small vessels in the region of the macula Friedenwald and Friedenwald[58] point out that at times these are the only vessels in the retina to show definite changes which is perhaps correlated with the fact that they are the smallest arterial vessels that can be seen ophthalmoscopically (internal diameter 10 to 15 microns according to Friedenwald and Friedenwald)

5 Changes in the color of the arteries and in the brightness and width of the reflex stripe have been attributed significance for the diagnosis of retinal arteriosclerosis Appearances characterized as copper-colored and silver wire arteries are not uncommonly seen as a result of changes in the walls Increased brilliancy and broadening of the reflex stripe are sometimes considered as evidences of retinal arteriosclerosis but normal variations in these respects are so great that the Friedenwalds consider the findings of no clinical significance Irregularity of the reflex is of more importance for the recognition of arteriosclerosis

Ophthalmoscopic Findings in Arteriosclerotic Retinopathy.—Retinal arteriosclerosis of marked degree can be present for years without producing ophthalmoscopically discernible changes in the fundus. In other cases, however, the vascular lesions do result in changes in the retina which may be characteristic and striking.

The papilla is rarely involved, which is of great importance for the differentiation of arteriosclerotic retinopathy from hypertensive retinopathy. In unusual instances, especially when cardiac failure is present, there may be some haziness of the margins of the disk, but this is not marked. In rare cases of long duration arteriosclerotic atrophy develops.



FIG. 9.—Arteriosclerotic retinopathy in essential hypertension. The papilla is unaffected. There is a venous closure above. (Courtesy of the late Dr. Robert K. Lambert.)

In the retina, hemorrhages constitute the most common finding; they may be few or many in number, superficial or deep, rounded, linear or irregular in shape. The hemorrhages are often accompanied by white spots, especially the cases in which the latter are prominent were formerly confused with hypertensive retinopathy. But while in hypertensive retinopathy the exudates may have either the soft appearance described as cotton wool or be hard and sharply delimited, in arteriosclerotic retinopathy the white areas are hard, sharply delimited, and often shiny; edema evidently plays little part in their production. The color varies from dead white to yellowish. The white spots vary greatly in number; most often there are none or few, but in exceptional instances they are very numerous. As a rule the individual areas of degeneration are small.

but there may be a few large lesions. In some instances the spots have an irregularly stellate or circinate arrangement in the macular region. Choroidal sclerosis with pigment changes is often to be seen.

Although retinal arteriosclerosis is bilateral, the resulting changes in the retina are not uncommonly unilateral for a long period, as was true in 45 per cent of Moore's cases. In consequence of formation of new lesions and disappearance of old ones, especially hemorrhages but occasionally also white spots, the picture may vary greatly from time to time.

The effect on vision is of course dependent on the location of the lesions and the occurrence of complications. Among the latter are thrombosis of a central vessel, optic atrophy, glaucoma and, what is extremely rare, transitory blindness due to arterial spasm. It need scarcely be added that hypertensive retinopathy not uncommonly develops in a retina already the seat of arteriosclerotic changes.

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Chapter

13

THE SUBDIVISION OF BRIGHT'S DISEASE

Before Bright — Every discoverer has his precursors and Bright was no exception. It was pointed out in Chapter 6 that the association of diseased kidneys with dropsy had been noted by isolated observers beginning with ancient times. These individual observations however influenced neither the practice nor the theory of medicine. The first real step in the study of the pathological states later described by Bright was the discovery by Cotugno[1] that the urine of dropsical patients is albuminous. Cotugno arrived at this important finding in the following curious manner. He had observed that the fluid of dropsical effusions is coagulable by heat. Cotugno had further noted that the absorption of such effusions is accompanied by increased urinary output and therefore believed that the dropsical fluid is eliminated through the urinary passages. To test this theory he investigated if the urine of such patients has the same property of coagulation by heat as the effusion and found that such is actually the case.

Toward the end of the same century Cruikshank[2] found that albumin is not present in the urine of all dropsical patients. He stated that coagulable urine occurs only in individuals with general dropsy while the urine is free of albumin in those whose dropsy depends on unsound viscera, *e. g.* disease of the liver. Blackall[3] arrived at similar conclusions. About the same time Wells[4] carried out important studies on the urine of patients with scarlet fever. He found that the urine in postscarlatinal dropsy is often bloody. In other such edematous patients though the urine was free of blood corpuscles it was coagulated by heat so that he believed that it contained blood serum. Both Wells and Blackall observed lesions of the kidneys in some patients with dropsy and albuminous urine but in other cases they did not find these renal changes and were therefore unable to decide whether the albuminuria and dropsy were actually results of renal disease. During the same period Darwin,[5] Brande[6] and others studied albuminous urine but the investigations just cited represent the most significant work of the time in this field and undoubtedly laid the foundations for the epoch making investigations of Bright.

The Work of Bright — In 1827 Richard Bright[7]* lecturer on the Practice of Medicine at Guy's Hospital published the first volume of his *Reports of*

* For an appreciation of the personality of Bright as well as of his work which is and presumably always will remain the great classic of renal pathology and one of the milestones of all clinical medicine the reader is referred to the address delivered by Professor Thayer[8] on the occasion of the centenary of the publication of the *Reports of Medical Cases*. Dr Osman[9] has performed the valuable service of republishing in one volume Bright's original papers on renal disease.

Medical Cases containing the immortal description of "Cases Illustrative of Some of the Appearances Observable on the Examination of Diseases Terminating in Dropsical Effusion—and First of the Kidney." The fact of the association of dropsy, diseased kidneys and albuminous urine was demonstrated by masterly clinical descriptions of 24 such cases, in 18 of which the anatomical findings at necropsy were not only accurately described but illustrated by a series of color plates scarcely surpassed in the history of medical illustration. Bright confined himself to precise description of his remarkable observations at bedside and postmortem table, theorizing little and speculating not at all, with the result that surprisingly few of his statements are susceptible of adverse criticism in the light of present-day knowledge. He was helped by the chemical observations of his friend John Bostock, which are incorporated as letters in the *Reports*.

Bright differentiated three main groups among the cases of renal disease which he studied.

The first group includes cases in which "a state of degeneracy seems to exist. . . . This state of the organ is sometimes connected with a cachectic condition of body." From Bright's description and figures it is clear that at least some of the cases of this group were instances of amyloidosis.

The second form of diseased kidney is one in which the whole cortical part is converted into a granulated texture and where there appears to be a copious morbid interstitial deposit of an opake white substance. In this type Bright includes cases of glomerulonephritis in various stages; one is a typical example of acute glomerulonephritis.

The third form of disease is where the kidney is quite rough and scabrous to the touch externally, and is seen to rise in numerous projections not much exceeding a large pin's head, yellow, red and purplish. The cases he describes are instances of chronic glomerulonephritis with secondary contraction.

Bright was not altogether certain whether the three groups which he described were separate diseases or different stages of the same malady, though he evidently inclined to the former opinion. Thus he stated:

"Although I hazard a conjecture as to the existence of these three different forms of disease, I am by no means confident of the correctness of this view. On the contrary, it may be that the first form of degeneracy to which I refer never goes much beyond the first stage, and that all the other cases together with the second series and the third are to be considered only as modifications and more or less advanced states of one and the same disease."

Some of the numerous remarkable observations on symptomatology made by Bright will be mentioned in the individual chapters.

Bright's Followers. The Concepts of Parenchymatous and Interstitial Nephritis.—Despite some initial opposition on the grounds of the doctrines of humoral pathology—notably by Graves,[10] who doubted that the albuminuria results from the structural changes in the kidneys—Bright's description of renal disease as the cause of albuminuria and edema was quickly accepted. Bright and his contemporaries, especially Christison[11] and other members of the Edinburgh school, soon developed the clinical symptomatology of renal disease to a relatively considerable degree of completion. The

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THE SUBDIVISION OF BRIGHT'S DISEASE

Before Bright — Every discoverer has his precursors, and Bright was no exception It was pointed out in Chapter 6 that the association of diseased kidneys with dropsy had been noted by isolated observers beginning with ancient times These individual observations however influenced neither the practice nor the theory of medicine The first real step in the study of the pathological states later described by Bright was the discovery by Cotugno[1] that the urine of dropsical patients is albuminous Cotugno arrived at this important finding in the following curious manner He had observed that the fluid of dropsical effusions is coagulable by heat Cotugno had further noted that the absorption of such effusions is accompanied by increased urinary output and therefore believed that the dropsical fluid is eliminated through the urinary passages To test this theory, he investigated if the urine of such patients has the same property of coagulation by heat as the effusion and found that such is actually the case

Toward the end of the same century Cruikshank[2] found that albumin is not present in the urine of all dropsical patients He stated that coagulable urine occurs only in individuals with general dropsy while the urine is free of albumin in those whose dropsy depends on unsound viscera *e g* disease of the liver Blackall[3] arrived at similar conclusions About the same time Wells[4] carried out important studies on the urine of patients with scarlet fever He found that the urine in postscarlatinal dropsy is often bloody In other such edematous patients though the urine was free of blood corpuscles it was coagulated by heat so that he believed that it contained blood serum Both Wells and Blackall observed lesions of the kidneys in some patients with dropsy and albuminous urine but in other cases they did not find these renal changes and were therefore unable to decide whether the albuminuria and dropsy were actually results of renal disease During the same period Darwin[5] Brande[6] and others studied albuminous urine but the investigations just cited represent the most significant work of the time in this field and undoubtedly laid the foundations for the epoch making investigations of Bright

The Work of Bright — In 1827 Richard Bright[7]* lecturer on the Practice of Medicine at Guy's Hospital published the first volume of his *Reports of*

* For an appreciation of the personality of Bright as well as of his work which is and presumably always will remain the great classic of renal pathology and one of the milestones of all clinical medicine the reader is referred to the address delivered by Professor Thayer[8] on the occasion of the centenary of the publication of the *Reports of Medical Cases* Dr Osman[9] has performed the valuable service of republishing in one volume Bright's original papers on renal disease

causes secondary atrophy of the specific elements of the kidney. The clinical picture of chronic interstitial nephritis was dominated by cardio vascular phenomena, notably increased arterial tension, arteriosclerosis and cardiac hypertrophy, with marked tendency to cerebral hemorrhage.

The untenability of the separation of chronic parenchymatous and chronic interstitial nephritides was demonstrated by Weigert[1] in a primarily anatomical study. He pointed out that in all instances of parenchymatous nephritis interstitial changes are also present, and in the so-called interstitial nephritis the connective tissue proliferation is secondary to the changes in the renal parenchyma, just as is the case in cirrhosis of the liver. Weigert considered that in all cases the changes are primarily in the renal parenchyma.* Though the objections of Weigert were accepted as valid by most of the leading students of the time, the division of chronic Bright's disease into parenchymatous and interstitial nephritis became standard teaching and remained so until within recent years. It is, for instance, accepted in many editions of Osler's textbook. But at no time did this simple classification of chronic renal disease actually satisfy either clinician or pathological anatomist, and numerous attempts—the most notable in this country having been that of Delafield[2]—were made to classify more adequately the varieties of Bright's disease.

With the rise of bacteriology in the second half of the nineteenth century and the realization that some varieties of Bright's disease are consequences (albeit not always immediate) of infection, classification on the basis of etiology, obviously the ideal, began to be a possibility. Unfortunately, the etiology of the most common form of Bright's disease, essential hypertension, has remained shrouded in darkness. Early in this century the advent of "functional thinking" in organ pathology and the development of tests of renal function led to attempts to classify Bright's disease on the basis of the nature of the impairment of renal function. In France, for the first three decades of this century, the primary subdivision of nephritis was into salt retaining and nitrogen retaining forms. But it quickly became evident that various types of functional impairment of the kidney may be associated or succeed one another in the same patient, and that there is no necessary correlation between etiology and the nature of the derangement of renal function.

PRESENT DAY NOMENCLATURE AND SUBDIVISION OF BRIGHT'S DISEASE

It has long been evident that *the term Bright's disease represents no more than a historical concept.* Included in this eponymic designation are a multiplicity of totally independent nosologic entities which at one time or another were regarded as due to kidney disease and having in common one or more

* Present day knowledge, of course, renders untenable Weigert's conception that all forms of Bright's disease take origin within the renal parenchyma, i.e., within what is now known as the *nephron*. In the largest contingent of Bright's disease—that which starts with the clinical picture of essential hypertension—the damage to the nephron is secondary to changes in the renal arterioles. And the renal implication in chronic pyelonephritis starts between the nephrons and actually merits the designation chronic interstitial nephritis.

question that next engaged some of the best medical minds of the time and called forth an enormous literature was one that had perplexed Bright namely, whether the variegated anatomical and clinical pictures described by Bright correspond to different diseases or are merely successive stages of one and the same process

In France, Rayer[1] maintained that Bright's disease is an inflammation of the kidney which he termed albuminous nephritis* (*nephrite albumineuse*) but differentiated six varieties of this inflammation Frerichs,[13] one of the outstanding German clinicians of the post Brightian period, likewise considered Bright's disease to be a single inflammation of the kidney and recognized three stages An initial hyperemia, a secondary period of exudation with fatty degeneration of the renal epithelium, and a third stage of connective-tissue hyperplasia terminating in atrophy of the kidney This unitaristic interpretation of Bright's disease had many adherents for a long period

It was however quickly recognized by a number of observers that Bright's disease really includes several distinct entities The independence of the amyloid kidney and of chronic passive congestion of the organ with albuminuria and cylindruria resulting from cardiac failure was admitted and adequate clinical criteria for their differentiation elaborated by Traube[14] The plural nature of the other varieties of Bright's disease was also maintained by various observers, notably English clinicians Thus Johnson[15] differentiated a number of diseases on the basis of the state of the renal epithelia Wilks[16] also upheld strongly the view that different diseases are comprehended under the term Bright's disease He writes that Among these were two very remarkable extreme conditions—the one a kidney large and white often double the natural size and associated with a very considerable dropsy of the whole body the other a kidney, hard and contracted often only half the natural size chronic in character and often destitute of symptoms Gull and Sutton's[17] and Ziegler's[18] emphasis of the significance of the arteriolar lesions in causing the contracted kidney also helped to establish the heterogeneous nature of Bright's disease The pluralistic conception of Bright's disease was likewise strongly advocated by Grainger Stewart[19] who entitled his monograph Bright's Diseases

In accord with the findings of Wilks and especially as a result of a systematic treatise by Bartels [20] it became customary during the third quarter of the past century to consider chronic Bright's disease as consisting of two varieties chronic parenchymatous and chronic interstitial nephritis Chronic parenchymatous nephritis was described as consisting in an inflammation of the epithelial cells of the kidney which in accord with Virchow's conception of parenchymatous inflammation went through stages of cloudy swelling fatty degeneration and finally disintegration The clinical manifestations of parenchymatous nephritis were notably renal edema oliguria and marked albuminuria Chronic interstitial nephritis on the other hand was thought to consist in a primary proliferation of the interstitial connective tissue of the kidney which by pressure

* So far as I am aware this is the first use of the term nephritis to designate the diseases described by Bright

results from the complication of essential hypertension by inflammatory nephritis a conception which they later abandoned (p 821) *

Nosology and Terminology in This Book —It was mentioned above that Bright's disease represents no more than a historical concept which includes a diversity of diseases They have in common only that the kidney is diseased at some stage of their evolution** and that the clinical picture includes one or more of the manifestations—edema proteinuria or hypertension (cardiac hypertrophy)—which Bright observed in his original case The diseases in question are so heterogeneous that at present a faultless classification based on a unitary criterion does not seem feasible With this limitation in mind the following classification and nomenclature will be used in this book Like the classification of Volhard and Fahr it is based on the pathogenesis of the renal lesions

The Forms of Bright's Disease

Orthostatic proteinuria intermittent venous hyperemia of the kidney

Nephrosis non inflammatory lesions of the nephron
- Necrotizing nephrosis
  - Chemical origin
  - Circulatory origin (prerenal azotemia)
  - With tubular obstruction
- Chronic nephrosis (lipoid nephrosis)
- Diabetic glomerulosclerosis (Kimmelstiel Wilson syndrome)
- Renal amyloidosis
- Specific toxemia of pregnancy

Nephritis inflammatory lesions of the kidney
- Glomerulonephritis
- Focal glomerular lesions of subacute bacterial endocarditis
- Wire loop glomerular lesions of disseminated lupus erythematosus
- Focal nephritis
- Acute interstitial nephritis
- Pyelonephritis

Essential hypertension arteriolosclerotic lesions of the kidney (at advanced stage)

These entities will be characterized in the individual chapters Here however a few preliminary comments may not be amiss

The term nephrosis has been deprecated as an etymological monstrosity meaning full of kidney However Allen[27] quotes from Webster's Inter-

* Addis[30] introduced a terminology based on Volhard and Fahr's classification which has been used by some others Corresponding to Volhard and Fahr's nephritis nephrosis and sclerosis Addis spoke of hemorrhagic degenerative and arteriosclerotic Bright's disease While this terminology has the virtue of simplicity it will be noted that the first variety is defined on the basis of a symptom hematuria while the other two are characterized by the nature of the morbid process in the kidney

** But the patient may succumb before there is demonstrable renal involvement While an individual in the malignant phase of essential hypertension would undoubtedly have been regarded by Bright as suffering from the disease described in his masterpiece essential hypertension may terminate from cerebral hemorrhage before the microscope shows renal changes

of the clinical and anatomical characteristics described by Bright. Differentiation of these individual forms of Bright's disease resulted from many widely separated investigations. These studies will be considered in the individual chapters. Among them the following may be mentioned here as having contributed notably in the separation of the entities collectively designated as Bright's disease.

1. In 1872 Gull and Sutton[17] showed that in some types of Bright's disease the primary anatomical changes are located in the arterioles and capillaries of the kidney and other organs. They designated the process as arterio-capillary fibrosis. Later Allbutt and Huchard (*cf.* Chapter 24) showed that in at least many of these cases hypertension antedates the anatomical changes, and what is now known as essential hypertension was recognized.

2. In 1879 Langhans[3] found in an anatomical study that one variety of Bright's disease starts with inflammation of the glomeruli alone. He termed this disease glomerulonephritis. Glomerulonephritis was known from the start to be a consequence of infection, which subsequent studies showed to be almost always streptococcic.

3. In 1905 Friedrich Mueller[4] pointed out the desirability of separating the primarily degenerative from the inflammatory lesions of the kidney. He proposed that the term nephrosis be used to designate the primarily degenerative forms of renal disease.

Volhard and Fahr's Pathogenetic Classification.—These differentiations were integrated into Volhard and Fahr's pathogenetic classification of Bright's disease. A pathogenetic classification is based on the nature of the pathological processes occurring in the diseases under consideration. Of necessity such a classification includes a large anatomical element, for the location of the morbid changes must also be considered. A pathogenetic classification that received wide acceptance was developed by Franz Volhard and Theodor Fahr, the one a clinician and the other a pathological anatomist, who published in 1914 a brilliant monograph[5] on Bright's disease which marks one of the great milestones in knowledge of the field. They suggested the following pathogenetic system:

Volhard and Fahr's Classification of Bright's Disease.—A. Degenerative diseases (*nephroses*) with or without amyloid degeneration of the vessels. Subvariety: Necrotizing nephroses.

B. Inflammatory diseases (*nephritides*).
  1. Focal nephritides.
    (a) Focal glomerulonephritis.
    (b) Septic (interstitial) focal nephritis.
    (c) Embolic focal nephritis.
  2. Diffuse glomerulonephritis.

C. Arteriosclerotic diseases (*scleroses*).
  1. Benign hypertension.
  2. The combination form: Sclerosis plus nephritis.

It will be noted that pyelonephritis is not included in the above classification; the importance of this condition was not recognized at the time. By the combination form Volhard and Fahr meant what is now known as malignant hypertension; they believed at the time that this clinical picture

19 STEWART *Practical Treatise on Bright's Diseases of the Kidney* 2nd ed Edinburgh 1871
20 BARTELS Ziemssen's *Cyclopedia of the Practice of Medicine* English translation New York vol 17 1877
21 WEIGERT Volkmann's Sammlung klin Vortraege Nos 162 and 163 1879
22 DELAFIELD Tr Assn Am Phys 6 125 1891
23 LANGHANS Virchow's Arch f path Anat 76 85 1879
24 MUELLER Verhandl deutsch Path Gesell 9 64 1905
25 VOLHARD and FAHR *Die Bright'sche Nierenkrankheit* Berlin 1914
26 ADDIS J A M A 85 163 1925 ADDIS and OLIVER *The Renal Lesion in Bright's Disease* New York 1931
27 ALLEN *The Kidney* New York p 207 1951

national Dictionary that one meaning of the suffix osis is "an abnormal or diseased condition" To the writer it seems that a generic term for the non-inflammatory lesions of the nephron is needed, and nephrosis serves this purpose adequately The use of the word myocarditis to designate not only the rheumatic and other true myocarditides but also the clearly degenerative lesions resulting from obstruction of the coronary arteries was long a roadblock to the undertsanding of cardiac disease, and the same has been true of the use of nephritis for both inflammatory and non inflammatory lesions of the kidney It will be noted that nephrosis is defined as designating the non inflammatory lesions *primarily involving the nephron* and thus does not include the regressive changes secondary to arteriolosclerosis Further, the term non inflammatory is used the word degenerative, originally used by Friedrich Mueller is not applied because some of the characteristic changes—notably the appearance of lipids and hyaline protein droplets in the tubular epithelia—are doubtless not always regressive in nature but manifestations of storage

Chronic (lipoid) nephrosis, the wire-loop lesions and focal nephritis have not been universally accepted as nosologic entities The reasons why they are so considered in this book are given in the individual chapters

The term malignant hypertension does not appear in the above list The reason is that the available evidence indicates strongly that malignant hypertension is a syndrome which may complicate any disease with diastolic hypertension provided the latter is high enough (*cf* p 822)

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In previous editions of this book and by others the term *benign albuminuria* was used to include not only orthostatic proteinuria but also the not rare instances of proteinuria in childhood without typical relation to posture and not at the time demonstrably due to renal disease. However the experience of the past fifteen years has convinced the writer that in other than typical orthostatic proteinuria one can not predict with certainty the subsequent course of any proteinuria in childhood. Even minimal proteinuria discovered incidentally in a school examination with little abnormality in the sediment without history of antecedent infection and no subjective symptoms may prove to be a manifestation of chronic glomerular nephritis. For this reason the term benign proteinuria should be used only for the demonstrably orthostatic cases.

THE OCCURRENCE OF ORTHOSTATIC PROTEINURIA

Orthostatic proteinuria occurs predominantly in the second half of childhood and adolescence. While cases have been reported as early as the second year (Jehle[11]) they are rare before the sixth year then increasing in frequency to attain a maximum at the time of puberty. An extensive investigation of the incidence of proteinuria was carried out by [illegible][12] whose findings are summarized by Calvin, Isaacs and Meyer[13] in the following table

		Percentage				
Age years	No. of children	Albuminuria	Boys with albuminuria	Girls with albuminuria	Trace of albumin	2+ or more
6 to 7	1946	6.7	5.0	8.5	5.6	0.2
10 to 11	1350	2[illegible].0	18.0	35.5	15.6	5.7
15 to 16	2481	38.0	29.5	46.0	25.5	3.2

Saito[14] found proteinuria in 1[illegible] per cent of 140 healthy schoolboys and Langstein[15] in 12 per cent of children over five years of age treated in the dispensary. On the other hand Hamill and Blackfan[16] showed that if the urine is examined repeatedly the incidence of proteinuria is much higher. They found protein at one time or another in 88.7 per cent of 124 children between the ages of eighteen months and fourteen years. The acetic acid body was present in 85.4 per cent and albumin in 27.4 per cent of these urines. Orthostatic proteinuria is much less common in adults than in children but is not rare particularly in young adults. We have mentioned above the findings of Leube and Maclean which revealed that about 5 per cent of healthy soldiers have proteinuria. It might be thought that benign proteinuria would be more common in soldiers than in others for standing at attention causes a lordosis which is a factor in the production of proteinuria in susceptible individuals (see below). However Diehl and McKinlay[17] found almost the same incidence of proteinuria in male students at the University of Minnesota: 5.32 per cent of 20,000 students had albumin in the urine on the examination of a single specimen with the nitric acid ring test. Of those with such a single positive test only 11.8 per cent

Chapter

14

ORTHOSTATIC PROTEINURIA

Not long after Bright's discovery of the relations between renal disease and proteinuria, observations were made of individuals who, despite proteinuria of many years duration, *showed no impairment of health*. As early as 1841 Becquerel[1] described a man who had proteinuria but was otherwise healthy. Vogel noted that such harmless proteinuria is apt to be present during the day and absent at night. In 1873 Sir William Gull[3] stated that boys about the age of puberty frequently had albuminuria, becoming languid, weak and pallid; he did not know the cause of the proteinuria.

The attention of the profession generally was first called to the frequency of proteinuria not due to any demonstrable organic disease in 1878 by the publications of Moxon[4] and Dukes[5] in England and Leube[6] in Germany. Moxon described the occurrence of "chronic intermittent albuminuria" in individuals, particularly adolescents, in whom there was no other evidence of renal disease. Analogous observations were made by Dukes on boys at Rugby. Leube found that of 119 healthy soldiers about 4 per cent had protein in the urine passed on rising in the morning and that this incidence rose to 12 per cent after marching. The amount of protein was small in all instances, not exceeding 0.1 per cent. He was unable to find evidence of renal or other disease in any of the men exhibiting proteinuria. Similar results were obtained by Maclean[7] in an extensive investigation during World War I. He found that about 5 per cent of 50,000 soldiers in training had protein in the morning urine. Exercise increased the incidence of proteinuria in one group of 200 men from 7 to 14 per cent.

Pavy[8] found that proteinuria in children and young adults without renal disease is not constant but occurs in cycles. The protein is absent in the first urine of the morning, quickly appears during the morning and then diminishes, often to vanish completely until it reappears the next morning. He therefore termed the condition cyclic albuminuria. Soon after, Sterling[9] made the important observation that the appearance of the protein is connected with the assumption of the erect posture and used the expression postural albuminuria. The importance of the change from the reclining to the erect posture is emphasized in the expression now generally used, orthostatic albuminuria, introduced by Teissier.[10] Because the urinary *protein may include serum globulins* as well as albumins, the term orthostatic proteinuria will be used in this book.

demonstrated in all cases Saito[14] found 90 per cent of not demonstrably nephritic proteinuria between the ages of ten and fourteen years to be of the orthostatic type On the other hand Hamill and Blackfan did not encounter typical orthostatic behavior even once in 124 children of whom 89 per cent had proteinuria at one time or another a finding which is not in accord with the results of other investigators and certainly not with my experience Calvin Isaacs and Meyer found most of their cases not to be orthostatic Jehle points out however that careful study is often necessary to demonstrate the orthostatic nature of the proteinuria the technique devised by him will be described in discussing the diagnosis Using such precise methods the marked influence of change in posture has been demonstrable in my experience in the large majority of children with proteinuria not accompanied by other evidences of renal disease

While in some instances the proteinuria is very constant being present every day in others it is highly irregular vanishing and reappearing for no obvious reason

An important feature of orthostatic proteinuria is the presence of considerable quantities of the acetic acid body (see p 120) in almost all instances Serum albumin is also present Wallis[4] who believes the acetic acid body to be euglobulin found the albumin globulin ratio in the urine in benign proteinuria to be but 2 a much lower ratio than is usually found in organic disease of the kidney In cases in which he brought on the proteinuria suddenly Jehle found that serum albumin appeared in the urine ten or twenty minutes before the acetic acid body could be demonstrated

It was formerly believed that casts do not occur in benign proteinuria but it is now known that hyaline and even granular casts in renal epithelia in small numbers are often to be found in the sediment of the centrifugalized urine A few red cells may also be present These microscopic findings which can often be observed in perfectly healthy individuals do not speak against the diagnosis of orthostatic proteinuria I have repeatedly seen them in classical cases Rytand[4] has found that the urine passed in the erect posture sometimes contains large numbers of casts and renal epithelial cells Calcium oxalate crystals are a common finding as already noted by Pavy Heubner[20] states that in girls nearing puberty it is very common to find large masses of vaginal epithelium which disappear when the proteinuria clears up

At the height of the proteinuria there is more or less marked oliguria and usually a diminution in the chloride content of the urine (Loeb[3]) the other urinary constituents being present in normal amount These changes are those which would be expected in slight circulatory stasis It is to be emphasized that *in orthostatic proteinuria tests of renal function performed in the usual way show no functional impairment of the kidney* However Rytand found in two subjects with orthostatic proteinuria that the urea and creatinin clearances in the erect posture were only one half as great as when recumbent Bull[1] observed that during the proteinuria renal blood flow and glomerular filtration are diminished and the filtration fraction is increased There is no nitrogen retention in the blood The plasma proteins are also normal (Swanson and Schultz[6]) The extrarenal

showed persistent proteinuria and only 6.5 per cent had evidence of probable kidney disease. In 4500 persons aged between fourteen and seventeen years, who were examined for occupational fitness, Nowak[18] found orthostatic proteinuria in 524, i.e., 11.6 per cent. King and Gronbeck[illegible] calculated that of 75,000 cases in the literature of the age of inductees, 3.3 per cent had proteinuria. Pavy's oldest patient with cyclic (orthostatic) albuminuria was forty-nine years of age. I have seen orthostatic proteinuria in the thirties, and once in a man of fifty with a marked spinal deformity.

As far as sex is concerned, the statistics of Lauener and of Calvin, Isaacs and Meyer show benign proteinuria to be more frequent in girls than in boys, the latter authors finding protein about twice as often in the urines of girls.

An interesting observation, which accords with the great discrepancies between different statistics of the frequency of benign proteinuria, has been made by Ashburn.[19] In an investigation on West Point cadets, he found that the incidence of benign proteinuria varies greatly in different years, at times assuming almost epidemic proportions. The cause of these fluctuations was not clear and confirmation would be desirable.

THE CLINICAL PICTURE OF ORTHOSTATIC PROTEINURIA

In many instances the proteinuria follows the characteristic cycle mentioned above. The first urine of the morning, if passed before the patient has left bed, is free of protein. During the early morning hours protein appears, quickly reaches a maximum, and then diminishes as the patient goes about during the day. By evening it has often disappeared completely. This cyclic occurrence is, however, not an essential characteristic of the proteinuria but is due, as shown by Stirling and Heubner,[illegible] to the fact that the proteinuria is provoked by the assumption of the erect posture and the ordinary habits of life involve rising in the morning. If a person with orthostatic proteinuria stays in bed all day and rises toward evening, the proteinuria will appear at that time. Heubner showed that the appearance of protein is due to the actual act of assuming the erect posture, so that the maximum amounts of protein are found if the first urine formed after rising is examined. Afterward the quantity diminishes. Jehle[1] found as high as from 0.4 to 1.2 per cent of protein in the urine formed shortly after standing, while examination of the total day's urine of the patient showed only a minimal amount of protein. Most often the amount of protein lost in the urine is insignificant from the point of view of the organism as a whole. However, Peters and Van Slyke[illegible] have found as much as 3 grams of protein in the twenty-four-hour urine of apparently healthy young adults. Moving about tends to diminish the proteinuria; standing erect, as in the military position of attention, to increase it. The effect of posture on the proteinuria will be discussed further in connection with the pathogenesis.

There is no general accord as to what portion of the not demonstrably nephritic proteinurias of childhood is of the orthostatic type, i.e., induced by the erect posture. Jehle believes that the influence of posture can be

moval of foci of infection but from the writer's experience this was probably coincidence In France the view was quite widely held that the benign proteinurias are often indicative of a tuberculous infection and the term pretuberculous albuminuria (Teissier) applied to them As a matter of fact however children with orthostatic proteinuria show no special predisposition to tuberculosis

Undernutrition has also been considered as a contributory factor in the production of benign proteinuria But it is evidently not a sufficient cause in itself for Jehle noted that in the period of undernutrition in Vienna during the first World War there was no increase in the incidence of benign proteinuria despite the fact that those diseases in which undernutrition is a contributory factor such as tuberculosis increased tremendously

There is no evidence to support the view held by some writers that benign proteinuria is due to changes in the blood proteins It was mentioned above that Swanson and Schultz found the blood proteins normal in orthostatic proteinuria and the writer has repeatedly made the same observation

Early observers noted that many of those with benign proteinuria present what they regarded as evidence of *constitutional inferiority* for which reason the term constitutional albuminuria was applied to the condition by Martius[31] Among 171 children with benign proteinuria Martius found only 8 who were not in some way what he regarded as constitutionally inferior to the writer Martius's criteria for constitutional inferiority would seem to exempt few children from this designation Speaking in favor of a constitutional factor in the pathogenesis of orthostatic proteinuria is the not rare familial occurrence Munk[34] studied a family in which 4 of the 5 children had orthostatic proteinuria in each instance beginning about the eighth year and Wetherbee and Foley[32] observed orthostatic proteinuria in homologous twins However a specific constitutional anomaly has not been established as the basis of orthostatic proteinuria After a review of the extensive older literature on the relation of constitutional types to benign proteinuria Bauer[3] came to the conclusion that there is no specific and characteristic anomaly resulting in orthostatic proteinuria The latter has been described as more common in children of asthenic habitus and this has seemed to be true in the cases which I have seen Bull[5] on the contrary noted no correlation between postural proteinuria and body build Orthostatic proteinuria has been observed in association with congenital heart disease The suggestion of retarded development of the kidney (Teissier) is unsupported by cogent evidence

Lordosis —While it has been known since Stirling's (*loc cit*) paper that in many cases of benign proteinuria protein appears in the urine only when the patient is in the erect posture no plausible explanation of this phenomenon was advanced until the publications of Jehle[25] beginning in 1908 Jehle made the interesting and important observation that most of those with orthostatic proteinuria have when in the erect posture a well marked lordosis the deepest part of which is at the level of the first and second lumbar vertebrae This lordosis disappears when the patient reclines Jehle was able to show further by a beautiful series of observations that

symptoms so often associated with renal disease, edema and hypertension, are always absent. Bass and Wessler [7] have found that the blood pressure of children with orthostatic proteinuria does not differ significantly from that of other children.

Most children with orthostatic proteinuria do not appear robust. They are usually pale, even though there is no actual anemia, and often look pasty. The usual history is that they have been considered "delicate" and are weak and nervous, often suffering from headache and sometimes having vomiting spells. They are often apathetic, avoiding strenuous games and exercise. Pollitzer [8] stated that a dry cough is commonly present but I have not observed cough, which was perhaps due to a high incidence of juvenile tuberculosis in the Vienna of the time. The musculature seems hypotonic and circulatory asthenia is often evidenced by cold extremities with patchy cyanosis. The carriage is often poor, there being a well marked lordosis in the lower thoracic and upper two lumbar segments and frequently a protuberant abdomen (pot belly). Varicocele is not rare. The proportion of children with orthostatic proteinuria who appear emotionally labile is high—some perhaps as a result of the reactions of the parents to the discovery of the proteinuria. But none of these findings is constant, and orthortatic proteinuria is often encountered in vigorous and sturdy children appearing the picture of health. The constitutional peculiarities which have been considered as associated with benign proteinuria will be considered in the next section.

THE PATHOGENESIS OF ORTHOSTATIC PROTEINURIA

The question why protein should appear in the urine of individuals presenting no other evidence of disease has called forth a voluminous literature, in which unfortunately hypotheses have far outnumbered facts.

The view that orthostatic proteinuria is in reality a manifestation of true chronic nephritis was defended by Johnson [9] and others since. However, this conception is disproved by the fact that these individuals never show any of the typical manifestations of renal disease such as edema, hypertension or impairment of renal function, even though they are followed for many years (see below). Maclean's (*loc. cit.*) extensive experience during World War I showed that soldiers with benign proteinuria had no greater incidence of trench nephritis than other soldiers. Heubner [6] reported an autopsy on an individual with orthostatic proteinuria who died of an intercurrent cause, so far as I am aware the only one in the literature. There was no evidence of renal disease.

Another factor which has been considered as playing a part in the causation of some cases of benign proteinuria is focal infection, particularly in the lymphoid tissue of the throat, the teeth and the accessory sinuses of the nose (Pollitzer, Calvin, Isaacs and Meyer). But as the latter investigators point out, it is improbable that such chronic infections are ever the *sole* cause of benign proteinuria. For we see many patients with severe infections who have no proteinuria and, on the other hand, many with benign proteinuria have no evidence of focal infection. Calvin, Isaacs and Meyer have seen the proteinuria in some instances clear up after the re

tion by the left kidney which became larger However the proteinuria does not always come solely from the left kidney Bull found that of 18 patients with postural proteinuria who had been cystoscoped including 3 of his own the proteinuria was *bilateral* in 8 and 1 had proteinuria only from the right kidney

The above observations demonstrate that in many cases of orthostatic proteinuria the exciting cause of the proteinuria is an accentuated lumbar lordosis which appears when *the individual* stand up But it seems improbable that pronounced lordosis is concerned in the production of other cases of benign proteinuria For one thing not every child with benign proteinuria has a well marked lumbar lordosis though the majority do Moreover that lordosis in itself *need not produce proteinuria* is shown by patients with extreme lumbar lordosis due to for example poliomyelitis muscular dystrophy or hip joint disease most of whom have no proteinuria whatsoever (Lewison Freilich and Ragins[39])

However in *other such cases there is proteinuria influenced by posture* Long before Jehle s work Bartels[40] gave a detailed description of a patient with muscular atrophy who had an extremely marked lordosis in the erect posture which was corrected when he reclined *Bartels observed* that this patient had proteinuria when erect but the protein disappeared from the urine when the patient reclined

Deficiencies in the General Circulation.—Deficiencies in the general circulation have long been thought by some to be *concerned in the production* of orthostatic proteinuria Some of the patients have striking vasomotor instability and there may be abnormally great acceleration of the pulse on changing from the reclining to the erect posture I del[41] called attention to the fact that the appearance of protein is accompanied by oliguria and that as the protein disappears the urinary volume rises Various cardiac types have been described Thus Lommel[42] found cardiac hypertrophy 38 times among 90 individuals with orthostatic proteinuria On the other hand Reyher[43] found the drop heart to be the most common form Politzer reconciles these differences by his observation that in these cases the heart is abnormally *mobile* so that it appears small in the erect posture and larger when reclining In a careful investigation Bass and Wessler[27] found that while a considerable proportion of their cases had evidence of relative cardiovascular insufficiency these symptoms were not associated in the great majority of cases with any hypertrophy or dilatation of the heart Thirty per cent of their patients had drop hearts I have seen no evidence of cardiac hypertrophy many of the children have an overacting heart during the examination which in combination with the thin chest wall may have simulated cardiac hypertrophy in the eyes of older clinicians

Erlanger and Hooker[44] carried out very detailed studies of the circulation on a patient aged twenty seven years with typical orthostatic proteinuria They demonstrated clearly that in this case the proteinuria was dependent on circulatory conditions

Erlanger and Hooker found that when their patient was raised from the recumbent to the erect posture protein first appeared in the urine when the body had attained an angle of 40 degrees If they eliminated the effect of

in many cases the production of a lordosis in the erect posture is the reason for the orthostatic nature of the proteinuria. *When the child* is in bed there is neither lordosis nor proteinuria. If the child rises from bed lordosis appears and with it proteinuria. Should the child stay on its knees, a position in which lordosis is very marked, the proteinuria is especially pronounced. On the other hand the proteinuria disappears if the child when standing, *puts one foot on a stool* which eliminates the lordosis despite the retention of the erect posture. Also, if the lordosis is corrected by means of an appropriate frame, there is no proteinuria in the erect *posture. But if the* lordosis is produced while the child is in bed by putting pillows under the back proteinuria appears. Jehle quotes some interesting *examples of how* lordosis produces proteinuria in susceptible individuals. Thus, he observed one child in whom protein appeared every morning while still in bed; this was due to the fact that she combed her hair while in bed, *an action that produces a marked lordosis*. When her hair was combed by another person the proteinuria disappeared.

Jehle states that lordosis of the type he describes is found only at the time of life at which orthostatic proteinuria usually occurs. He believes *the lordosis is produced* by the vertebral column growing more rapidly than the rest of the body. Jehle found that while in normal children the distance from the vertebra prominens to the end of the sacrum is almost exactly one third of the total length of the body, the length of the vertebral column in children with orthostatic proteinuria exceeds this proportion by several centimeters. He believes that in individuals with weak muscles and lax ligaments this disproportionate length of the vertebral column readily leads to a lordosis. In several children with orthostatic proteinuria Jehle observed that the excessive length of the vertebral column later became compensated by faster growth of the rest of the body, at which time the proteinuria disappeared.

Sonne[36] has made some interesting observations which afford support to Jehle's view of the significance of lordosis in the production of orthostatic proteinuria. He catheterized the ureters of 6 individuals with orthostatic proteinuria, the catheters remaining in place while the patient was either erect or a lordosis was produced in the recumbent posture. In 1 instance there was complete anuria for forty minutes, in 3 others left-sided anuria, while in the remaining 2 the urine from the left kidney was albuminous, in 1 instance containing as much as 2.6 per cent of protein. In no case was the urine from the right kidney albuminous. In 2 patients with orthostatic proteinuria whom I also saw, Beer[37] also proved cystoscopically that the protein in the urine came solely from the left side. It will be remembered that inasmuch as the vena cava lies to the right of the mid line, the left renal vein crosses over the vertebral column, from which it is separated by the aorta, a relatively hard structure. For this reason Kelling[38] pointed out that if lordosis affects the kidneys through mechanical interference with the venous return, the left kidney might preferentially suffer. Sonne's observations bear out this line of reasoning. It is also afforded some support by the studies of Rytand[24]. In two of his subjects with orthostatic proteinuria diodrast appeared normally in both kidneys in the supine position; when they were erect the diodrast was excreted in low concentra-

cases of renal disease which for long periods show no symptoms other than proteinuria and slight microscopic urinary abnormalities a type of case that is not uncommon in childhood It is to be remembered that protein uria in organic renal disease may show postural variations increasing in the erect posture It is not uncommon in patients convalescing from post scarlatinal glomerulonephritis for the urine to be free of protein while the patient is in bed but albuminous when he rises As Russell[18] emphasizes all varieties of proteinuria may be influenced by posture In proteinuria of nephritic origin however the quantity of protein in the urine is usually distinctly increased by exercise while in orthostatic proteinuria there is as a rule less protein when the patient walks about than when he stands still But the difference is rarely great enough to be of practical value

The relations of the proteinuria to posture may be studied as follows Let the patient empty his bladder an hour after going to bed so that no urine formed while still erect should be included in the morning specimen When the patient wakes the next morning let him pass urine while still in bed this is free of protein in orthostatic proteinuria Then have the patient get out of bed and either stand at attention or even better on his knees for about ten minutes these positions bring about a marked lordosis The urine then passed should contain protein if the patient has orthostatic proteinuria If a patient with orthostatic proteinuria goes about all day it will usually be found that the urine passed in the evening has less protein than in the morning a phenomenon which is the reverse of the rule in nephritic proteinuria

One should be very hesitant in diagnosing benign proteinuria if the twenty four hour urine contains more than a small amount of protein While the urine elaborated immediately after assuming the erect position may contain large quantities of protein (rarely even 1 per cent) in orthostatic proteinuria this does not continue and the total day s urine rarely contains more than 0 2 or 0 3 per cent of protein and usually considerably less Large amounts of protein in the twenty four hour specimen speak strongly for organic disease

In benign proteinuria there is usually marked precipitation with dilute acetic acid in the cold But inasmuch as this reaction is absent in some cases of benign proteinuria and is not uncommon in organic renal disease it is of little diagnostic value

The urinary sediment in benign proteinuria contains comparatively few or no casts and at most a few red blood cells Only if the subject stands in a position of exaggerated lordosis can quite numerous hyaline and granular casts and even a moderate increase in the number of erythrocytes be brought out Large numbers of casts or many red cells therefore speak strongly for organic renal disease But it is to be remembered that there may be very few casts in proteinuria due to true nephritides

THE PROGNOSIS OF ORTHOSTATIC PROTEINURIA

The prognosis of orthostatic proteinuria is unconditionally good Many individuals who had orthostatic proteinuria in childhood have been examined in later life by Dukes[16] Heubner[18] and others In the vast majority

gravity by having the patient stand in water or exerted a pressure of 50 mm of mercury on the lower extremities by means of pneumatic trousers, there was no proteinuria in the erect posture These experiments indicate the significance of circulatory factors in the production of the proteinuria The investigators showed that increase in general venous pressure did not produce the proteinuria by having the reclining patient breathe against a high pressure until there was marked cyanosis proteinuria did not appear Erlanger and Hooker were further able to show that any procedure that lowered the pulse pressure favored the appearance of proteinuria in this patient, while any measure that increased the pulse pressure caused the proteinuria to diminish In connection with this finding they stress the conception that in experiments pulsatile filling of an organ is more efficient than constant filling and that the glomeruli are particularly adapted to pulsatile filling

However interesting as are the results obtained by Erlanger and Hooker in this patient they evidently do not explain most cases of orthostatic proteinuria for Bass and Wessler [7] found that there is little difference between the blood pressure of children with orthostatic proteinuria and normal children I have seen no evidence that deficiencies in the general circulation play any part in the causation of orthostatic proteinuria

General Discussion —Orthostatic proteinuria results from an impediment to the venous return from the kidneys which is present in the erect posture and disappears during recumbency In many cases the venous engorgement which produces the proteinuria is confined to the left kidney and results from compression of the left renal vein against the aorta by lumbar lordosis which is accentuated in the erect posture In others the lordosis compromises the inferior vena cava with resultant bilateral venous engorgement and proteinuria Bull[51] has made observations which he interprets as indicating that the compression of the inferior vena cava by the lordotic spine is against the posterior surface of the liver

The causative lordosis is apparently of constitutional origin and correlated with the period of rapid growth in height it almost invariably disappears after this period There may be other mechanisms (*e g* ptosis) which kink a renal vein in the erect posture and thus produce proteinuria but these are not yet understood There is no evidence that infection plays any part in the pathogenesis of orthostatic proteinuria

THE DIAGNOSIS OF ORTHOSTATIC PROTEINURIA

The diagnosis of benign proteinuria is of the highest importance so that true nephritides may not be neglected or what is surely much more common healthy children be subjected to unnecessary restraint which interferes with their normal development Unfortunately the differentiation of orthostatic proteinuria from organic renal disease is often a matter of great difficulty requiring a long period of observation In many cases which ultimately clear up one is never sure with which he is dealing

The presence of arterial hypertension edema or impaired renal function speaks immediately for the diagnosis of an organic lesion of the kidney The difficulties lie in the differentiation of orthostatic proteinuria from those

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of the cases the proteinuria had disappeared. None of these studies afford any evidence that orthostatic proteinuria leads to disease of the kidney later in life. Jehle states that in only 3 cases of a very extensive experience did he observe orthostatic proteinuria become continuous, but does not mention that actual symptoms of renal disease developed. Fox[47] found no evidence of subsequent renal disease in any of the 20 cases of orthostatic proteinuria that he detected during life insurance examinations, though 13 of them were examined as long as thirty years after the proteinuria was originally detected. Maclean's[7] extensive investigation during World War I showed that recruits with benign proteinuria did not have a higher incidence of trench nephritis than other troops. Orthostatic proteinuria must therefore be considered as harmless in its influence on the duration of life and the subsequent state of the kidneys.

This view has been adopted by life insurance physicians. Thus Gulland[48] states that if the proteinuria is orthostatic he does not rate the applicant up. Fox[47] also accepts applicants with benign proteinuria at ordinary rates for a twenty-five-year policy, but asks a small advance for a whole life policy. In the writer's opinion this is unjustified.

It is impossible to answer with any assurance the usual question of parents of children with orthostatic proteinuria as to how long the proteinuria will last. All that can be told them is that no matter how long it lasts it will never do any harm and will ultimately disappear. In some cases the condition clears up soon after being noted, but in the majority it does not disappear until during or shortly after puberty. Cases are known in which the proteinuria has been followed for as much as fifteen years after puberty (Martius[31]), but such a long duration seems to be unusual. When the orthostatic proteinuria noted in young adults had its inception has not, to my knowledge, been investigated.

THE TREATMENT OF ORTHOSTATIC PROTEINURIA

Once the diagnosis of orthostatic proteinuria has been established, the patient needs no treatment. Above all, neither rest nor dietetic treatments should be attempted. It is highly improbable that they exert any favorable influence on the proteinuria. The child should be allowed to play in the open and eat just as other children do. It may be difficult to reassure the parents to prevent their coddling the child with the inevitable deleterious effects of such a procedure. Neurotics must not be created. In the vast majority of instances, the child would undoubtedly be better off if the proteinuria were never discovered.

If the child has a marked lordosis, exercises designed to strengthen the trunk muscles may be prescribed, but in general the best exercise is normal play. Jehle has designed a frame to correct the lordosis. I have not seen the device used, but it seems totally unnecessary in view of the harmlessness of the proteinuria. Wearing such an apparatus may create a feeling of inferiority in the child with consequences infinitely worse than those of the proteinuria.

Nassau,[49] Post and Thomas[50] and others have found that alkalinization of the urine with sodium bicarbonate will often cause the proteinuria to

disappear But the proteinuria returns if the alkalinization is discontinued so there would seem to be no object in the procedure Atropine calcium and other substances have been stated to diminish the proteinuria but are of no practical utility Moreover in several children with classical orthostatic proteinuria to whom I gave enough sodium bicarbonate to alkalinize the urine there is was no definite effect on the amount of protein excreted

Concomitant conditions such as infected tonsils carious teeth or the frequent anemia of obscure origin should receive attention But this should be done only for the same indications as in children without orthostatic proteinuria for there is no evidence that focal infections have any relation to the latter or that their removal will render the urine noncoagulable

It is more difficult to decide what to do in the cases in which the protein uria greatly diminishes but does not completely disappear in the horizontal position and the differential diagnosis between orthostatic proteinuria and renal disease rests uncertain Such patients should be kept under observation for a protracted period until a decision can be reached There seems to be no good reason for putting them to bed or keeping them from school during the period of observation While efforts should be made to minimize exposure to inclement weather and respiratory infection and perhaps oral prophylactic doses of penicillin administered one should be careful not to induce an anxiety state in the child or its parents

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Chapter

15

THE NECROTIZING NEPHROSIS

During recent years, three circumstances especially have combined to widen interest in a family of nephropathies characterized clinically by an acute course with extreme oliguria and anatomically by necrosis of the tubular epithelium

1 More frequent transfusion has unfortunately brought in its wake an increase in the number of individuals receiving incompatible blood

2 Sulfonamide therapy introduced a potent and for a time common source of renal tubular damage

3 The battle injuries and civilian bombings of World War II furnished an enormous contingent of patients with renal damage consequent on trauma Indeed it was Bywaters and Beall's[1] description under the name of the *crush syndrome* of post traumatic anuria following injuries in the London Blitz that focused the attention of the profession generally on the kidney diseases here under discussion

In an important study of the extensive material of World War II at the Army Medical Museum Lucke integrated the different etiologies of acute renal necrosis under the designation *lower nephron nephrosis* Lucke coined this term because he found that the same regressive lesions in the lower nephron which Dunn and his coworkers[3] had originally observed in the crush syndrome occur as a result of a variety of etiologies severe trauma to muscle nontraumatic muscular ischemia burns transfusion with incompatible blood heat stroke blackwater fever toxemias of pregnancy and uteroplacental damage alkalosis sulfonamide intoxication and poisoning with certain vegetable and chemical agents By lower nephron Lucke means the ascending (thick) limb of Henle's loop and the distal convoluted tubule The term lower nephron nephrosis has attained wide currency However in the following the term *necrotizing nephrosis* will be used because the circumstances have not yet been established in which the damage is actually confined to the lower nephron For instance in hemoglobinuric nephrosis which has been reckoned as a lower nephron nephrosis the proximal convoluted tubule may be most severely affected In burns Martineau and Hartman[4] find the proximal convoluted tubule necrotic even more often than the loop of Henle By all odds the most direct technique available for the localization of lesions in the renal tubule is Oliver's beautiful method of microdissection of entire nephrons and their study in continuity By this method Oliver[5] has shown that *the disruptive changes may involve any segment of the nephron* (cf p 411)

Nor are definite clinical criteria as yet available for the differentiation of lesions of the individual segments of the tubule The clinical picture of

necrotizing nephrosis due to mercury poisoning, which affects predominantly the proximal convoluted tubule, does not differ from that of post traumatic anuria in which the lesions may affect any part of the tubule For these reasons the term lower nephron nephrosis does not seem adequately based

The *necrotizing nephroses* are many and diverse But while the etiologic varieties have individual clinical and anatomic characteristics, there are fundamental features common to all

Clinical Picture — The clinical picture of all forms of necrotizing nephrosis is dominated by rapidly progressive impairment of renal function An outstanding characteristic is an early and abrupt fall in urinary volume,

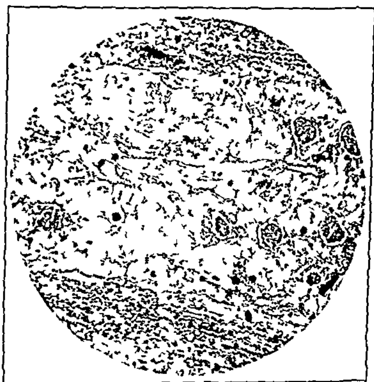


Fig 10 — Necrotizing nephrosis with secondary calcification complicating peritonitis The calcified masses appear black

which often goes on to anuria In the necrotizing nephroses of renal origin *e g*, mercury poisoning hyposthenuria is present from the onset Contrariwise in those renal necroses which are of prerenal origin *e g* traumatic shock the specific gravity is high during the initial stage of isolated impairment of glomerular filtration and then falls as the tubules are damaged The renal failure produces uremia However uremic symptoms may become distressing only after a deceptive latent period of several days during which the patient feels well Hypertension is absent at the onset but often appears after several days while often only modest exceptionally it exceeds 210/120 mm Edema generally is absent unless considerable volumes of fluid are administered The mortality is considerable in most

forms of necrotizing nephrosis. If recovery is to occur it is most often heralded by increase in urinary volume which may go on to tremendous polyuria. Hyposthenuria may last for months during which the patient feels well. The writer has not encountered any cases in which it seemed clear that necrotizing nephrosis went on to chronic renal disease, either death or complete recovery has occurred. However, the possibility that necrotizing nephrosis may lead to chronic renal disease has *not been excluded* and *further* observations regarding this possibility are desirable. In cases succumbing in the second week fibroblastic activity may be prominent which suggests that with survival scarring would result.

An excellent and detailed study of the clinical picture of *necrotizing* nephrosis has recently been published by Swann and Merrill.[122]

Pathological Anatomy. —The characteristic lesions are regressive changes in the tubular epithelia which go on to necrosis. Various segments may be affected predominantly. Individual parts of the tubule may be affected with selective intensity in the different etiologic varieties of necrotizing nephrosis but much remains to be learned of the topographic characterization of each of the latter. After the first days *reparative proliferation* of the tubular epithelial cells *becomes evident*. Tubular obstruction by casts is extensive in some *but* not all varieties of necrotizing nephrosis. *Intertubular* edema and cellular infiltration often develop secondarily. Glomerular lesions are not prominent but frequently *the presence of* protein in Bowman's space bespeaks increased *permeability* of the loops.

Understanding of the *morphological* characteristics of the necrotizing nephroses has been greatly furthered by the recent investigations of Oliver and his coworkers.[5] They applied Oliver's technique of *microdissection* of individual nephrons and their study *in continuity*. This method renders feasible much more accurate localization in the nephron than does the study of histological sections. Oliver found that two types of renal lesion occur *in the conditions* of acute renal failure here under discussion. "The first is a nephrotoxic necrosis limited *to that part of the* nephron, the proximal convolution, which is *functionally* concerned with the handling of the poison. Since poisons *are* distributed by the renal circulation all *nephrons* are equally involved. The second type of lesion is a disruption of the renal tubule (tubulorhexis) due to focal cortical ischemia. It occurs at random among nephrons and in any *part of a nephron*. Oliver's *preparations* show clearly that *in this* second lesion there is solution of the *continuity* of the tubular wall by discrete and more or less numerous *and* extensive foci of epithelial necrosis with rupture of the underlying basement membrane. He observed that the tubular cells *may* be remarkably well preserved *right* up to the necrotic *segment*. For many features of the morphology of the necrotizing nephroses *which* are revealed only by study *of* individual nephrons in continuity, the reader is referred *to the* unique publication of Oliver *and* his associates, which to the *writer* seems a classic of the *morphology* of the diseased kidney.

Pathogenesis and Pathological Physiology. —Four main processes enter into the pathogenesis *of the* necrotizing nephroses:

1. Decrease in renal blood flow of prerenal *origin* with resultant slowing of glomerular filtration and ischemic damage to the renal epithelia.

2 Injury to the tubular cells by substances entering them from the glomerular filtrate or blood stream Included are not only readily diffusible bodies such as mercuric chloride or sulfonamides, but also such large molecules as hemoglobin and its derivatives, which are taken up by the tubular cells and damage them by mechanisms yet to be elucidated That it is predominantly the entry into the tubular cells of such substances as mercuric chloride from the glomerular filtrate rather than from the blood stream which is responsible for the epithelial damage is shown by experiments in which filtration in one kidney is stopped by ureteral ligation, the necrotizing nephrosis then affects only the contralateral organ

3 Blockage of tubular lumens by such substances as heme pigments or sulfonamide crystals which either form large conglomerates or so increase the viscosity of the tubular fluid as to impede its flow

4 Secondarily to the tubular damage there occur edema and sometimes cellular infiltration of the intertubular tissue The resultant swelling and increase in intrarenal pressure may be significant in decreasing renal blood flow and consequently glomerular filtration (*cf* Peters[6])

The importance of these factors doubtless varies greatly in individual necrotizing nephroses and in different stages of the same process Thus, in traumatic shock decrease in renal blood flow with slowing of glomerular filtration inaugurates the pathogenetic chain tubular damage with hyposthenuria follows only later Contrariwise in mercury poisoning solely the factor of damage to the tubular epithelia operates at the start only later does swelling interfere with the renal circulation

Characteristic of the renal insufficiency in necrotizing nephrosis—and hardly if at all encountered in other conditions—is that augmented and nonselective tubular back-diffusion is *one* of the participating factors * In the chemical nephroses augmented back diffusion is doubtless the *initiating* factor in the pathogenesis—leading to what was above called regurgitation uremia (p 37) Richards[7] demonstrated this by direct observations on frogs poisoned with mercury He observed that filtration continues at a rate even faster than normal but no urine issues from the tubules apparently all the filtrate is drawn through the necrotic tubular walls back into the blood by the osmotic pressure of the plasma proteins Dyes to which the tubular cells were normally impermeable entered these cells from the lumen after they had been poisoned by mercury Hayman[8] and his coworkers demonstrated the occurrence of tubular back-diffusion in dogs in whom necrotizing nephrosis had been produced by uranium salts They found that the inulin and creatinin clearances and extractions were greatly depressed although renal blood flow (measured by the Fick principle from the renal arterio venous creatinin and inulin differences) were only negligibly changed In some of their observations there was a

* The anatomical basis for the regurgitation of tubular fluid into the blood in necrotizing nephrosis is revealed by the above-mentioned investigations of Oliver[4] by microdissection of individual nephrons The following is his description As one follows the course of the intact tubule quite suddenly a place is found where the basement membrane is broken frayed or disintegrated and the epithelial lining disrupted and necrotic The result is a solution of continuity The lumen thus lies open to the intertubular interstitial tissue and its capillaries and veins

negative diodrast Tm (p 38) i e more diodrast was filtered than was excreted thereby demonstrating the tubular back-diffusion of this substance which is normally excreted with remarkable efficiency by the tubules It was mentioned above (p 52) that a few observations have been recorded of a negative Tm in human necrotizing nephrosis Unfortunately these findings of a negative Tm have been obtained by clearance methods which lack absolute validity in the presence of tubular necrosis (p 24) but they nevertheless indicate strongly that tubular back-diffusion has occurred

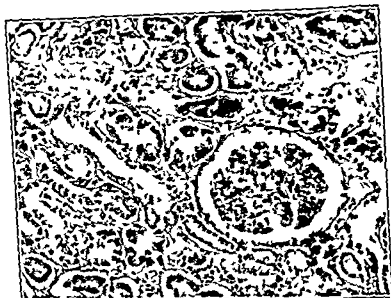


Fig 11 —Necrotizing nephrosis in a postoperative patient who succumbed with renal insufficiency (oliguria going on to anuria NPN 200 mg per cent terminally uremic frost)

Decrease in kidney blood flow also participates in producing the renal insufficiency of necrotizing nephrosis It is the primary factor in necrotizing nephrosis of prerenal origin (p 79) but also occurs in the later stages of the chemical nephroses Since the glomeruli show little change fall in renal blood flow presumably occurs when swelling of the kidney due to intertubular edema and cellular infiltration elevate intrarenal pressure But obstruction of tubules by casts may also participate through producing internal hydronephrosis of the affected nephrons which hampers renal blood flow and impedes glomerular filtration Decreased renal blood flow was demonstrated in experimental mercury poisoning by Linder and Sarre[8] The clearance studies of Corcoran Taylor and Page[19] indicated decreased renal blood flow in human carbon tetrachloride and mercury poisoning By catheterization of the renal vein Sirota[11] demonstrated that renal blood flow and glomerular filtration are greatly diminished in the later stages of human carbon tetrachloride nephrosis His earliest

I am greatly indebted to Dr William Antopol Director of Laboratories of Beth Israel Hospital for Figures 11 1? 18 27 33 34 35 and 49

measurements were eight days after the onset of oliguria, in 1 case renal blood flow was only 40.8 cc per minute. In 33 patients with necrotizing nephrosis due to ingestion of poisons, intravascular hemolysis, shock and other causes Bull, Joekes and Loew[12] studied renal blood flow by PAH clearance and renal vein catheterization. They found renal blood flow grossly reduced during the oliguria, with improvement, it then steadily increased and reached normal levels in from three to nine months. In these observations glomerular filtration showed reduction of the same order as blood flow. That all the functions of the tubule are depressed in necrotizing nephrosis, as would be anticipated from the anatomical findings is indicated by these studies of Bull, Joekes and Loew with renal vein catheterization and clearance methods. During the oliguric phases of necrotizing nephrosis, they found inability of the kidney (1) to concentrate urea and creatinine (2) to conserve sodium, chloride and potassium (3) to extract PAH from the blood and (4) to reabsorb glucose at a normal rate."

In most instances of necrotizing nephrosis two stages of impairment of renal function succeed one another (1) An initial *oliguric stage* due to excessive passive back-diffusion of filtrate and perhaps decreased glomerular filtration and (2) a *diuretic stage* due to impairment of active tubular reabsorption.

Long after symptomatic recovery from necrotizing nephrosis evidence of damage to tubular function persists. There may be hyposthenuria for months or even more than a year. Hunter and Muirhead[133] observed 2 cases in which salt wastage lasted for forty four and sixty days after the onset the total urinary chloride excretion varied between 20 and 48 grams of NaCl. It is important that this salt losing tendency be combatted during convalescence.

MERCURIAL NEPHROSIS

As far back as 1519 Ulrich von Hutton[13] was aware that mercurial intoxication may be manifested by anuria. Up to twenty years ago mercury poisoning was a common cause of necrotizing nephrosis. But with the replacement in New York City at least of bichloride of mercury by barbiturates as the favorite means of committing suicide mercurial nephrosis has become infrequent. The outspoken clinical or anatomical picture of necrotizing nephrosis hardly occurs in chronic mercurial intoxication, being seen after a single large dose of bichloride of mercury taken by mouth either accidentally or with suicidal intent or vaginally as a douche or abortifacient. However Munk's[14] observation that calcified foci are not uncommonly found in kidneys of old syphilitics indicates that the therapeutic use of mercury can cause similar lesions though of slighter degree. Rarely calcific foci are also present in the kidneys of patients who have had mercurial diuretics.

Pathological Anatomy —In fatal cases of mercurial nephrosis the kidneys are enlarged smooth and soft. As a rule they are grayish white and anemic but Askanazy and Nakata[15] state that in the rare cases that die within the first day after the poisoning and those succumbing after the eighth day, the kidneys may be red and congested.

Microscopically the picture is dominated by necrosis of the tubular epithelium The proximal convoluted tubules are selectively implicated in the necrosis While there may be lesser involvement of other segments of the tubule it is not nearly as severe as the necrosis of the proximal tubule * The necrotic cells are swollen and converted into granular masses staining deeply with eosin in which the nuclei cannot be seen Bell[18] states that careful examination reveals that a thin basal portion of most of the cells is intact this layer contains the nucleus and thus offers the possibility of regeneration The lumen of the tubule is often completely obliterated by the necrotic cells Other cells show extreme cloudy swelling and vacuolar degeneration with extensive desquamation but there is little or no fatty change The patent tubular lumens often contain casts

The glomeruli usually appear normal apart from frequent congestion But on closer examination some swelling and less often foci of necrosis and desquamation of the capsular epithelium may be observed

A remarkable phenomenon is the calcification of the necrotic epithelial cells long ago described by Saikowsky[19] It is present in most though not all cases in which death occurs after the first days Calcification of the renal epithelia is not diagnostic of mercury poisoning it occasionally also occurs in intoxication by bismuth and other chemicals When intestinal obstruction or other causes of prerenal azotemia (Chapter 3) are accompanied by renal necrosis some of the tubules may be calcified Zeman and his associates[9] observed calcification as early as the second day of necrotizing nephrosis in experimental pyloric obstruction in cats Among the other causes of calcification of the renal tubules listed by Derow[21] are Vitamin A deficiency ingestion of an excess of inorganic phosphate hyperparathyroidism and excessive injections of viosterol In mercurial necrosis the calcification occurs principally in the convoluted tubules and ascending limb of Henle's loop the calcified masses staining deep blue with hematoxylin Contrary to most varieties of calcification the calcium is present as the phosphate only (Wells[22]) Calcified casts may be found

The cause of the extensive calcification in mercurial nephrosis which is much greater than in necrotizing nephrosis due to other heavy metals is not clear It is not due to increased calcium content of the blood for this is not present The normal or low calcium concentration in the blood also speaks strongly against the hypothesis of Schmidt[23] who attributes the renal calcification to the frequently coexistent mercurial colitis which throws a heavier burden in calcium excretion on the kidney

After mercurial nephrosis has been present for about three days regeneration of the epithelial cells begins (Heineke[24]) The newly formed cells first appear as flat elements under the old necrotic cells and may proliferate so as to surround the latter completely The regenerated cells stand out in the section because of their deeply staining nuclei They may form giant cells Heineke believes that the regenerated epithelia participate in the removal of the dead cells Around the necrotic masses are also polymorphonuclear leukocytes which evidently act as phagocytes Removal

* Injection of mercury into various mammals and the frog likewise produces selective necrosis of the proximal tubule (Suzuki[16] Edwards[17])

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Red blood cells are most often scanty or absent but may at times appear in moderate numbers in the sediment Nor are leukocytes conspicuous

The volume of urine diminishes and in many cases complete anuria develops quickly not a drop of urine can be obtained by catheterization In other instances the anuria is *interrupted only* by the formation at intervals of small quantities of urine such as 50 or 100 cc The anuria may continue for several days until improvement is heralded by the appearance of urine or death from uremia occurs

The predominant mechanism in the pathogenesis of the oliguria and renal insufficiency is doubtless nonselective back-diffusion of the glomerular filtrate through the necrotic tubular wall

During the first days of the anuria or extreme oliguria there is often a deceptive latent period as in obstructive anuria during which the patient feels well and is even euphoric In other instances he is tortured by mercurial stomatitis or colitis But if the flow of urine is not reestablished the picture becomes that of typical uremia with the symptomatology described in Chapter 7 Edema is rare unless *it is produced* by *the forcing of fluids* it was present in but 1 of Rosenberg s [7] 14 cases The absence of edema demonstrates clearly the incorrectness of the view once widely held that tubular injury causes edema *Hypertension is* absent in some cases but in others the blood pressure rises after oliguria has been extreme for three or four days to as high as about *170/100 mm* as in other forms of necrotizing nephrosis In one patient the blood pressure rose to 210/125 mm within four days The changes in blood chemistry are those found in all form of renal insufficiency (*Chapter* 3) The chloride content of the plasma unless influenced therapeutically is sometimes remarkably low (Lewis and Rivers [8] Kahan [9]) this is perhaps due to electrolyte loss from ulcerative lesions of the gastro-intestinal tract being added *to the uremic* vomiting Death is usually in uremic coma but may occur suddenly with manifestations of circulatory collapse and pulmonary edema

In cases which recover the formation of urine is resumed At first the volume is small but it quickly rises until large amounts even as much as 5000 cc or more daily are voided The urine is of low specific gravity even while the volume is small in view of the high concentration of potential urinary constituents in the blood this testifies eloquently to the severe injury to the concentrating power of the kidney Hyposthenuria may last for months after recovery

Diagnosis —This is usually obvious from the history In cases in which it is suspected that mercury has been taken for suicidal purposes the urine (if obtainable) and stools should be examined for mercury Lambert and Patterson[10] state that mercury appears in the urine in from three to twenty four hours after it has been swallowed

The postmortem demonstration of mercury in the organs may be of medico-legal importance It has been found that the kidneys contain the greatest concentration of mercury but that the largest absolute amount is in the liver (Sollman and Schreiber)

Prognosis —The outlook is largely dependent on the amount of mercury ingested and especially in recent years the rapidity with which treatment is instituted Formerly while most of those who took small amounts of

of debris and regeneration proceed very rapidly. Thus, in a case of bichloride poisoning studied by Hunter,[5] in which death occurred on the fourteenth day from pneumonia and the intestinal lesions, there had been almost complete regeneration of the tubular epithelium. In cases of some standing there may be a moderate degree of interstitial proliferation.

Clinical Picture.—The ingestion of large quantities of bichloride of mercury in tablets or solution is followed by a metallic taste in the mouth and abdominal pain. Usually there is vomiting, the vomitus often containing blood and mucus. In most cases stomatitis and bloody diarrhea with severe tenesmus then appear.

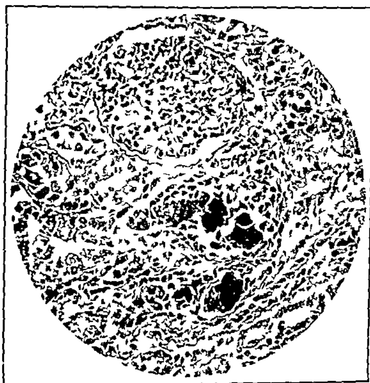


Fig. 12.—Necrotizing nephrosis with secondary calcification in mercury poisoning. The tubular cells are in various stages of degeneration and necrosis. The dark masses are calcified epithelia.

At any time from a few hours to about three days after the mercury has been taken, proteinuria and marked oliguria or anuria appear. In cases in which only small amounts are absorbed there may be proteinuria with polyuria. I saw one such case which quickly recovered.

After the proteinuria has appeared such little urine as is passed is generally cloudy. Hyposthenuria quickly appears and the specific gravity does not vary much from 1.010. The quantity of protein is rarely great and it may be only a small fraction of 1 per cent. Hyaline, granular and epithelial casts are present as well as numerous epithelial cells and granular debris evidently derived from necrotic cells. According to Munk[6] doubly refractile lipoids are never found in sharp contrast to chronic nephrosis

The antidotal effect of BAL is due to formation of a stable and relatively nontoxic compound with mercury which is rapidly excreted in the urine That BAL affords a high degree of protection against mercury poisoning was shown in experimental animals by Gilman et al [34] Stocken[36] and others Proof that BAL interferes with the effects of mercury on the tubular epithelium of the human kidney was afforded by the finding of Sussman and Schack[37] that it inhibits mercuhydrin diuresis The remarkable effects of BAL in bichloride poisoning in man were shown by the well controlled studies of Longcope and Luetscher While in 86 control patients who had swallowed 1 0 Gm or more of bichloride and were treated within four hours by conventional methods there were 27 deaths they had no deaths in 27 similar patients treated with BAL (cf also p 418)

It is of the utmost importance that BAL be injected promptly before there is irreversible damage to the kidneys The drug is supplied in 20 per cent benzylbenzoate in peanut oil and given intramuscularly The initial dose is about 3 mg /kg With desperately ill patients 5 mg /kg may be given The larger dose often produces transitory disagreeable by-effects such as nausea vomiting headache tremulousness and paresthesias BAL sometimes produces transitory hypertension in one patient the blood pressure briefly exceeded 200/100 mm Two mg /kg may then be given every four hours for several doses and followed by a similar dose once daily The tolerance of patients with mercury poisoning for BAL seems to be high, which has been attributed to combination of mercury and BAL in the form of a relatively nontoxic complex

In the general management of patients with mercurial nephrosis the same principles are followed as in other forms of acute renal insufficiency (p 225) Of primary importance is the alleviation of dehydration the tendency to which in mercurial nephrosis may be especially great because of vomiting and diarrhea due to ulcerative lesions of the gastro-intestinal tract But once dehydration has been relieved fluid and salt should be administered only in quantities sufficient to maintain the volume and composition of the extracellular fluid in the past forcing of sugar and salt solutions was often carried to the point of producing pulmonary and cerebral edema and heart failure Anemia is to be combatted by transfusion of blood and hypoproteinemia by plasma these should be carried out with especial caution because of the susceptibility of the patients to heart failure

The artificial kidney peritoneal lavage and other methods for augmenting extrarenal excretion are discussed on p 237

Decapsulation has been tried repeatedly in mercurial nephrosis though the success has been minimal In 53 cases collected by Hoffmann [12] in which decapsulation was performed for mercurial nephrosis only 2 recovered of about 30 such cases mentioned by Rosenberg [1,8] only 3 or 4 survived Though decapsulation is done only in very desperate cases these results do not seem better than those obtained by conservative measures even in the worst cases I have not seen recovery in mercury poisoning treated by decapsulation and do not advise the operation

Rybak and Stern[?] have observed the onset of diuresis in anuric cases of mercurial nephrosis following irradiation of the kidneys with small

mercury or were immediately effectively lavaged recovered (cf Lambert and Patterson,[30] Rosenberg[17]), almost all those who ingested large quantities succumbed unless they vomited the tablets or had them immediately washed out Thus Longcope and Luetscher[31] state that 8 of 9 patients who took 3 grams or more of mercuric bichloride and were not treated with BAL, died On the other hand all four of their patients who took 3 to 20 grams of bichloride and were treated with BAL recovered

Anuria is a serious omen However, even before BAL recovery had been observed after five or even more days of anuria While the onset of diuresis generally is followed by complete recovery, in rare instances death in uremia occurs This may be due to the urine being of such low concentration that increased volume does not avert renal insufficiency Salt depletion may participate in producing a fatal outcome during the diuretic phase

When recovery from mercurial nephrosis occurs, no permanent injury to the kidney seems to remain The proteinuria usually disappears within a few weeks but the impairment of concentrating power may last for months before it disappears completely

Treatment —The past few years have witnessed a gratifying improvement in the efficacy of treatment for mercurial nephrosis This is due primarily to the introduction of BAL But even before this there had been some improvement in the results because of better management of water and electrolyte balance

As quickly after the ingestion of the mercury as possible, the patient should be given several raw eggs in milk to precipitate any mercury in the stomach and the stomach washed thoroughly Sollman, Barlow and Biskind[3] point out that if milk is not available, it is advisable to administer half a glass of water before the eggs to prevent the latter from cementing the bichloride tablets to the stomach A vigorous cathartic should be given

Rosenthal[33] has introduced *sodium formaldehyde sulphoxylate* as an antidote for acute mercury poisoning This compound reduces bichloride of mercury to the mercurous form or metallic mercury If available sulphoxylate should be used for the initial lavage Rosenthal advises that the stomach be washed with a 5 per cent solution of sulphoxylate and about 200 cc of the solution left in the stomach Immediately after this 10 gm of sulphoxylate dissolved in 200 cc of water is given by very slow intravenous drip this may be repeated about six hours later If colitis develops Rosenthal gives high colonic irrigations once or twice daily with a 1 to 1000 solution of sulphoxylate The treatment is claimed to be effective when instituted up to about an hour and a half after ingestion of the bichloride On the basis of their animal experiments Brown and Kolmer[34] advise that smaller amounts should be given intravenously the main value of the sulphoxylate appears to be in its reducing action on the bichloride in the stomach and gut which it reaches by early oral administration

The treatment of mercurial nephrosis has been revolutionized by the introduction of British Anti Lewisite (BAL 2 3-dimercaptopropanol) This dithiol was originally introduced as an antidote for Lewisite and has proved to be the most effective available remedy for poisoning by arsenic, mercury gold and perhaps some other metals (but apparently not lead)

confronted predominantly by the manifestations of the necrotizing nephrosis. Hypertension is the rule and in rare instances exceeds 200/110 mm. Edema is generally due to forcing of fluids. There is oliguria which may progress to anuria. The urine contains protein, various types of casts and red and white blood cells; gross hematuria is exceptional. There is hyposthenuria. Cardiac insufficiency and pulmonary edema are always dangers. Renal retention may so overload the heart as to lead to high-output failure (Friedberg)[131]. Recovery is signalled by polyuria, but hyposthenuria may persist for months. Sirota's clearance studies showed evidence of functional impairment of the kidneys after almost a year.

In the 141 cases collected by Smetana there were 39 fatalities. However, lethal cases are more apt to be reported, so that the mortality rate is probably smaller.

Treatment.—After ingestion of the chemical the stomach should be washed out and a saline cathartic given. Respiratory depression may call for artificial respiration and injections of caffein sodium benzoate. Because of the liver damage, as much carbohydrate as possible should be given; parenteral administration is generally necessary. But because the chief danger to life is renal rather than hepatic failure, the advisability of attempting to give large amounts of protein and amino acids, as in other forms of liver damage, seems doubtful. The treatment of the acute renal insufficiency is discussed elsewhere (p. 223).

SULFONAMIDE NEPHROSIS

In the heyday of sulfonamide therapy, renal insufficiency was a redoubtable and not extremely rare complication which led to many deaths. The sulfonamides bring about renal failure through two mechanisms:

1. **Obstruction by Sulfonamide Crystals.**—Precipitation and conglutination of sulfonamide crystals may block the flow of urine anywhere from Henle's loop to the ureter; even vesical calculi may form. Crystals are rarely found proximal to Henle's loop where the major concentration and acidification of the glomerular filtrate occurs. By administration of sulfonamides to animals Antopol and Robinson[32] showed that precipitation and blockage may occur in a previously healthy urinary tract. There are four main factors which condition the likelihood of sulfonamide crystalluria.

(a) *The Blood Level.*—This is determined by the dose and the comparative rapidity of absorption and excretion. While there is no close parallelism between the amount of sulfonamide administered and the liability to urolithiasis, with sufficiently high doses of a drug no more soluble than sulfadiazine precipitation in the urinary tract is probably almost invariable unless the urine is alkalinized. This was indicated by patients in whom subacute bacterial endocarditis was treated by deliberate production of exorbitantly high sulfadiazine levels in the blood; pronounced azotemia almost always developed.

(b) *The Urinary Concentration.*—Oliguria with its entailed increase in concentration of the urinary constituents favors precipitation of sulfonamides. Crystalluria is hardly to be feared if the daily urinary volume

doses of roentgen rays I have no experience with the method of treatment which has no logical basis

CARBON TETRACHLORIDE NEPHROSIS

Necrotizing nephrosis due to inhalation or ingestion of carbon tetrachloride has been encountered with fair frequency in recent years since the chemical has been widely used as a cleaning fluid and in industry Alcoholism seems to favor the development of the intoxication The initial manifestations of acute poisoning are varied They may include nausea, vomiting and diarrhea the diagnosis of acute gastro-enteritis may be made in the absence of a history of inhalation or ingestion of the poison Sometimes there is vertigo lassitude and somnolence and the patient may be regarded as drunk Other early manifestations may be violent cough, headache convulsions, widespread bodily pains with muscular rigidity, or hematemesis Within twenty-four to forty-eight hours liver damage may be revealed by jaundice Oliguria sets in and uremic symptoms develop Sometimes a hemorrhagic diathesis appears Occasionally the initial symptoms are not pronounced or misinterpreted and the possibility of carbon tetrachloride poisoning is not considered until renal insufficiency is evident It is possible that the etiological role of carbon tetrachloride has been overlooked in some cases of necrotizing nephrosis (*cf* Farrier and Smith[38]) While many of the patients are desperately ill the large majority recover a fatal outcome is usually due to uremia Smetana[39] found symptoms of renal insufficiency in 33 of 141 cases of acute carbon tetrachloride poisoning and pointed out that the kidneys are more apt to be implicated when the poisoning is by inhalation

The *anatomical changes* are those of necrotizing nephrosis The glomerular tufts show little change Bowman s space is often widened and contains protein, the lining cells may be swollen The outstanding findings are regressive changes in the tubular epithelium going on to necrosis and desquamation There are large numbers of casts (not heme) and much epithelial debris in the tubular lumens In 2 cases carefully studied at necropsy by Smetana both the proximal and the distal segments of the tubules exhibited regressive changes but the necrotizing process was more severe in the distal portions There is intertubular edema and cellular infiltration In cases succumbing toward the end of the first week regeneration of tubular epithelial cells is evident

The detailed studies of Corcoran *et al* and Sirota on the *pathogenesis* of the renal insufficiency have already been mentioned (p 413) They indicate that both tubular function and renal blood flow are severely impaired Sirota s findings indicate that unselective tubular back-diffusion is the predominant factor in the earlier stages of the azotemia while subsequently decrease in renal blood flow (due to swelling) becomes more significant

The *clinical picture* is that found in all forms of acute renal insufficiency, complicated by the effects of carbon tetrachloride on the liver gastrointestinal tract and central nervous system as well as sometimes by a hemorrhagic diathesis However the symptoms other than those due to renal failure tend to clear up rapidly the result is that most often one is

confronted predominantly by the manifestations of the necrotizing nephrosis. Hypertension is the rule and in rare instances exceeds 200/110 mm. Edema is generally due to forcing of fluids. There is oliguria which may progress to anuria. The urine contains protein, various types of casts and red and white blood cells; gross hematuria is exceptional. There is hyposthenuria. Cardiac insufficiency and pulmonary edema are always dangers. Renal retention may so overload the heart as to lead to high-output failure (Friedberg).[30] Recovery is signalled by polyuria, but hyposthenuria may persist for months. Sirota's clearance studies showed evidence of functional impairment of the kidneys after almost a year.

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(b) *The Urinary Concentration.*—Oliguria with its entailed increase in concentration of the urinary constituents favors precipitation of sulfonamides. Crystalluria is hardly to be feared if the daily urinary volume

can be maintained above 1500 cc Many instances of sulfonamide blockage are due primarily to oliguria resulting from fever vomiting and inadequate fluid intake

(c) *The Reaction of the Urine* —Alkalinization of the urine averts crystalluria due to sulfadiazine or sulfathiazole Gilligan[40] and his associates observed that acetylsulfadiazine is 6 times as soluble at pH 6 5 as at pH 5 2 Fox[41] *et al* found that as the pH of the urine is increased there is a sudden great rise in the solubility of these sulfonamides and their acetyl derivatives when the urine becomes alkaline They state that this is because sulfadiazine and sulfathiazole as well as their acetyl compounds are weak and but slightly soluble acids which ionize and form soluble sodium salts in an alkaline medium On the other hand Fox and his associates found that sulfapyridine did not undergo extensive salt formation at any physiological pH which accounts for the failure of alkalinization to prevent precipitation of sulfapyridine

(d) *The Solubility of the Sulfonamide* —This is the most important factor Obstructive precipitation did not occur in the early days of sulfonamide therapy when the highly soluble sulfanilamide was used, but began to be encountered with the introduction of sulfapyridine and sulfathiazole which are but sparingly soluble in the acid urine and undergo a considerable degree of acetylation (largely in the liver) with the production of even less soluble acetyl conjugates When the somewhat more soluble sulfadiazine came into use it was hoped that obstruction by precipitated crystals would be eliminated but this hope proved illusory and many cases of fatal sulfadiazine urolithiasis were observed Lehr[42] attempted to prevent urinary precipitation by the introduction of sulfonamide mixtures He found that different sulfonamides are independently soluble in urine, so that more of a mixture (*e g* sulfadiazine sulfamethazine sulfacetamide and sulfamerazine) can be held in solution than of any one alone However the quantitative advantages of sulfonamide mixtures are not great and equal to alkalinization of the urine (Garb and Janoff[43]) Almost complete solution of the problem of precipitation has been achieved by the synthesis of highly soluble and therapeutically effective sulfonamides such as Gantrisin and sulfacetamide the latter is 80 times as soluble as sulfadiazine (Lehr[44]) Brinkhouse[45] *et al* treated 142 patients with Gantrisin and observed gross hematuria in 1 and crystalluria in 1 other Bigler and Thomas[46] detected neither crystals nor red cells in the urine of 71 children treated with Gantrisin

In the past few years renal insufficiency due to sulfonamide crystallization has become a rarity the writer has not seen a case in at least three years This is due partly to displacement of sulfonamides by antibiotics formerly when sulfonamides did not produce therapeutic results the dose was often increased despite acid oliguria and precipitation followed Even more important has been the introduction of the highly soluble sulfonamides and the appreciation of the importance of adequate urinary volume and alkalinization

2 **Necrotizing Nephrosis Due to Sulfonamides** —The symptomatology of urinary obstruction by sulfonamides with its renal colic and gross hematuria is often so spectacular that this was at first considered the only

pathogenesis of renal damage by sulfonamides. However it was soon pointed out by Long *et al*[47] that sulfonamides may produce renal insufficiency in the absence of obstruction by crystalline masses, as a result of cytotoxic action on the renal epithelia. Cases have repeatedly been observed in which renal insufficiency followed administration of sulfonamides and necropsy disclosed no evidence of *obstructive crystallization*. The writer has seen several such cases. In 2 patients with anuria due to sulfathiazole Prien[48] took renal biopsies during decapsulation with precautions to prevent solution of crystals but found none of the latter; there was focal necrosis of the tubules. In these cases the necropsy reveals only regressive changes in the tubular epithelia which go on to more or less widespread necrosis. Both the proximal and distal segments of the nephron may be implicated. In 12 cases studied by Bergstrand[49] predominantly the distal segments of the nephron were affected; the picture resembled that of the crush syndrome. Many of the tubular lumens contain masses of cellular detritus and homogeneous protein casts in which, at least in sections prepared by the usual techniques, sulfonamide crystals are generally not demonstrable. There is intertubular edema and cellular infiltration of varying degree. Minute granulomata composed largely of plasma cells and eosinophiles and sometimes containing giant cells may be seen (cf Lederer and Rosenblatt[50]). The glomeruli usually show little change.

Often doubtless both mechanisms operate. In one patient obstruction of both ureters by masses of sulfapyridine crystals was relieved by ureteral catheterization but renal insufficiency nevertheless progressed to a fatal termination. Necropsy disclosed tubular necrosis but no intratubular obstruction by crystals. In some cases of this type in which renal colic, gross hematuria and the presence of sulfonamide crystals in the freshly voided urine correctly leads to the diagnosis of damage by sulfonamide crystals, cytotoxic injury to the tubular epithelia is probably the more important factor in producing renal insufficiency and accounts for the lack of help from ureteral catheterization and pelvic lavage.

Lesions resembling those of acute glomerular nephritis and acute interstitial nephritis have been described in patients who became oliguric while taking sulfonamides (Murphy *et al*[51] Allen[52]) but that the sulfonamides and not the original infection was responsible remains to be proved. Hemorrhagic and necrotizing lesions of the calyces, pelvis and ureter may result from the crystalluria.

The *clinical picture* of sulfonamide nephrosis is akin to that of other forms of necrotizing nephrosis (p 410). There is oliguria which may go on to anuria and hyposthenuria. If the renal insufficiency is severe enough uremia results. Hypertension sometimes develops. The crystalluria may result in gross hematuria, renal tenderness and renal colic. However there are instances of renal damage by sulfonamides in which these manifestations of crystalluria are absent and which set in insidiously with oliguria only when the patient becomes nauseated, somnolent, disoriented or very weak despite disappearance of fever may suspicion be aroused that there is trouble other than that due to the original infection. When sulfonamide nephrosis produces severe oliguria the mortality is high although the writer is not acquainted with large statistics.

The *treatment* is that of acute renal insufficiency (p 223) Even though there are no obvious symptoms of crystalluria all patients should be cystoscoped, the ureters catheterized and the renal pelves irrigated with warm 2 5 per cent sodium bicarbonate solution An attempt should be made to alkalinize the urine by oral administration of sodium bicarbonate or intravenous injection of sodium bicarbonate or Hartman's solution Overly enthusiastic administration of sodium salts which may lead to heart failure, should be guarded against Actually there is no evidence that alkalinization in any way helps in sulfonamide nephrosis it is attempted in the absence of ureteral obstruction only because of the possibility that there may be intratubular obstruction by crystalline aggregates Rapid improvement has been observed to follow renal decapsulation (*cf* Prien[53]) but the operation has failed in other cases (2 seen by the writer many years ago) and its value is not proved

Other Chemical Nephroses —In addition to mercuric chloride carbon tetrachloride and the sulfonamides many other chemicals produce necrotizing nephrosis Among them are ethylene glycol (antifreeze *cf* Allen[54]) diethylene glycol (the poisonous constituent of the elixir of sulfanilamide which caused many deaths in 1937) tartrates chromates borates bismuth salts oxalic acid sulfuric acid hydrochloric acid arsphenamine and many others Many fatal cases of necrotizing nephrosis have been due to industrial or suicidal poisoning by these chemicals Experimentally uranium nitrate has been extensively used for the production of renal damage both tubular necrosis and glomerular lesions result (*cf* MacNider[55] and for a general review of experimental nephropathies Horn[56])

NECROTIZING NEPHROSIS DUE TO TRAUMATIC SHOCK (THE CRUSH SYNDROME)

It has long been known that oliguria is part of the clinical picture of shock That this oliguria is due to renal insufficiency was shown during World War I by observations that urea excretion in the urine is low (Richet and Flamant[57]) despite the presence of azotemia (Duval and Grigaut[58]) In many patients in shock renal insufficiency contributes significantly to the symptomatology and to the fatal outcome As a rule, renal function improves as shock clears But exceptionally such is not the case after disappearance of shock impairment of kidney function persists and may go on to fatal uremia Bywaters and Beall[1] observed in victims of crushing injuries during the bombardment of London that following recovery from shock the renal insufficiency may persist and some of the patients succumb to uremia even though the manifestations of shock have disappeared and the blood pressure risen to hypertensive levels Similar observations had been made in World War I (Minami[59]) and in civilian accidents (Husfeldt and Bjering[60]) But they attracted little attention and the interest of the profession in the remarkable persistence of renal insufficiency *after* recovery from shock resulted from the work of Bywaters and Beall Because most of their first patients had been crushed beneath fallen masonry or other heavy material they coined the designation *crush syndrome* However post traumatic uremia follows not only crushing injuries but also battle

wounds of all descriptions and the most varied civilian injuries, including those to the head

In civilian life clinically demonstrable necrotizing nephrosis follows traumatic shock in only an extremely small proportion of the cases In fact the sequence is distinctly a rarity which is doubtless the reason that so little was known of the crush syndrome prior to World War II Quite the opposite holds in war Mallory[61] found the lesion in 18 6 per cent of 427 unselected autopsies on battle casualties in Army hospitals in Italy Perhaps the main reason for the difference is that the battle casualties often cannot receive treatment for shock for a considerable time while in civilian life in recent years the period of shock following trauma has generally been enormously abbreviated by prompt administration of blood or plasma and other treatment Whether lesser degrees of renal damage quickly reversed with improvement of the circulation follow civilian trauma with greater frequency remains to be studied but seems probable in the light of the almost invariable oliguria in shock

Pathological Anatomy —The kidneys are usually enlarged and heavy weights of 400 or 500 grams are common and they may be even heavier The capsule strips with ease revealing a smooth and generally pale surface which may have shimmering areas The cut section is usually moist and may bulge over the edge of the capsule The cortex is usually pale and the medulla darker than usual in consequence the differentiation between cortex and medulla is sharp The Malpighian bodies are not prominent

Microscopically the changes in the *glomeruli* are rarely striking Often the only abnormality visible is the presence of protein in Bowman s space seen in the sections a eosinophilic precipitates of different size and texture The blood content of the loops varies sometimes ischemia is indicated by a paucity of red cells in the capillaries but in other cases they are well filled There is little change in the cellularity of the loops but there may be thickening of the walls akin to that seen in the toxemia of pregnancy (*cf* French[62]) so that the tuft has a solid appearance The epithelial cells of the parietal layer of Bowman s capsule may be heightened to a cuboidal form according to Bywaters and Dible[63] this metaplasia affects especially the part of Bowman s capsule adjacent to the mouth of the tubule Goormaghtigh[130] has described hypertrophy and increased granularity of the juxtaglomerular apparatus in the crush syndrome

The characteristic changes are in the *tubules* The epithelial cells are the seat of regressive alterations In cases succumbing in the first few days these may be limited to swelling increased granularity and a usually not prominent formation of lipid droplets In battle casualties Mallory[67] found the first morphologic change to consist in lipid vacuolization of the ascending limb of Henle s loop which appeared eighteen hours after injury These changes *per se* hardly enable the histological recognition of the nature of the process But they go on to the epithelial necrosis which constitutes the hallmark of the condition under discussion Necrobiotic changes in the epithelial nuclei are evident and the cells may disintegrate and appear as amorphous masses in the lumen or be desquamated *en masse* The necrosis is usually focal necrotic segments of the tubule are found next to others which have undergone little change Areas of tubular

collapse are common The necrotic tubule may undergo localized dilatation (herniation) or may rupture with extrusion of a cast or other content Such rupture was beautifully demonstrated by Oliver[64] by microdissection Dunn[3] observed that the necrotic segments are not rarely in apposition to veins, through the thin walls of which they may rupture and produce thrombosis While all divisions of the tubule may be affected, Bywaters and Dible and Lucke pointed out that the ascending limb of Henle s loop and the distal convoluted tubule are generally most severely affected It was this observation that led Lucke to coin the designation lower nephron nephrosis of which the crush syndrome is the paradigm However, it is to be emphasized that while the distal portions of the nephron are usually the most severely affected the proximal convoluted tubule is also implicated and may be the seat of widespread necrosis

Regeneration of the tubular epithelium starts within a remarkably short time and is often definite in cases which succumb in the second half of the first week The newly formed cells are flat elements which then become more cuboidal Lucke found that within ten days most of the damaged tubules are completely relined Regeneration thus becomes pronounced at about the time that diuresis is apt to set in if it does so at all

Often the feature that first strikes the eye on looking at the section through the low power is the filling of the tubular lumens by casts and debris In the upper parts of the nephron the tubular lumens contain precipitated protein identical with that in Bowman s space and debris of necrotic and desquamated tubular cells These may be agglomerated into dense hyalin, granular or epithelial casts Much more characteristic, however when present are the pigmented casts which occur in the more distal divisions of the nephron—the ascending limb of Henle s loop and the distal convoluted and collecting tubules They are brown in unstained preparations and usually copper-colored in hematoxylin-eosin section Bywaters *et al*[65] showed that these pigmented casts do not stain positively for free iron but that their tinctorial and spectroscopic reactions reveal heme pigment Since the urine contains myoglobin it may be accepted that the heme pigment is myoglobin although the appearance and staining reactions are the same as those of hemoglobin casts Heme casts are absent in some instances of crush syndrome and in others they are scanty Lucke found them only infrequently when survival was less than two days However, in other cases they are numerous and may be especially prominent in cross-sections of the papilla where massive granular or homogeneous brown casts may block most of the collecting tubules

In the later stages there exceptionally occurs dense leukocytic invasion of the tubules with an appearance like that of ascending pyelonephritis (Bywaters and Dible)

Surrounding the necrotic tubules are often foci of edema and infiltration with lymphocytes and histiocytes By the end of the first week fibroblastic activity may be evident and replacement of destroyed tubules by young scar tissue may already have started (Bywaters and Dible Lucke) Whether chronic renal disease ever takes origin in such a process is so far as I am aware not known

Pathogenesis —Clinical observation differentiates two stages of the crush syndrome

1 *Impaired Glomerular Filtration* —In the initial stages there is oliguria but no hyposthenuria In fact the small volume of urine passed may have a specific gravity exceeding 1 025 and a urea content of over 3 per cent These findings indicate that in this initial stage the impairment of renal function consists solely in slowing of glomerular filtration and tubular function is not yet significantly affected The decrease in glomerular filtration is a manifestation of shock the lessened cardiac output and the renal arteriolar constriction evoked by it diminish blood flow through the kidney and perhaps intra glomerular capillary pressure and thus lessen filtration That renal blood flow and glomerular filtration are diminished in shock proportionally even more than is cardiac output has been shown by clearance methods by Lauson Bradley and Cournand[66] The azotemia present at this stage is thus pathogenetically a prerenal azotemia and is discussed in more detail above (p 72)

2 *Impaired Tubular Function* —If improvement does not occur the oliguria is complicated by hyposthenuria The small volume of urine passed has a specific gravity close to 1 010 Impairment of tubular function has now been added to slowing of glomerular filtration and anatomical examination discloses the necrotizing nephrosis described above

The impairment of tubular function in turn passes through two stages (a) the oliguric or anuric stage in which nonselective back-diffusion of the glomerular filtrate through the necrotic tubule walls dominates (b) the polyuric phase in which the recovered or regenerated tubule cells prevent nonselective back-diffusion but have not yet recovered their normal functional capacity so that polyuria and hyposthenuria are present and the patient may suffer from or even succumb to salt and water depletion

Anatomically in 260 battle injuries Mallory found that oliguria and nitrogen retention precede the first recognizable morphologic changes These appear about eighteen hours after injury and consist in lipid vacuolization of the ascending limb of Henle s loop Only from the third day on did Mallory find tubular necrosis

The beautiful experiments of Van Slyke and his coworkers[47] point in the same direction They evaluated tubular function in dogs with hemorrhagic and traumatic shock by means of the para aminohippurate extraction (p 38) They found that PAH extraction decreases only after the renal blood flow has fallen below 5 per cent of normal So low a renal blood flow was attained in these experiments only after the hemorrhagic or traumatic shock had been maintained for several hours Van Slyke and his associates further found that while release of a clamp that has been on the renal artery of a dog for up to three or four hours is followed by gradual complete recovery of kidney function removal of the clamp after a longer period of complete ischemia results in irreversible renal damage with death from uremia in four to eight days

The evidence is very strong that the primary cause of damage to the tubular epithelia in the necrotizing nephrosis of traumatic shock is impairment of nutrition by decreased renal blood flow In his careful study of 260 battle injuries Mallory showed a close parallelism between depth of

shock and renal involvement The clearance measurements of Lauson *et al* (p 78) indicate a profound fall in renal blood flow in hemorrhagic and traumatic shock In these forms of shock in dogs, Van Slyke found that the functional accomplishment of the tubular epithelia measured by the PAH extraction (p 38), is reduced only when renal blood flow is reduced to less than 5 per cent of the normal value He also showed that clamping of the renal artery for two hours is followed by a protracted period during which functional depression of the tubule cells is documented by diminished PAH extraction, as mentioned above, if the artery was occluded for four hours the damage was irreversible and the animal succumbed to uremia in four to eight days as in human post-traumatic anuria

Of the primacy of decreased renal blood flow in the necrotizing nephrosis of traumatic shock there would thus seem to be little doubt But accessory factors may also be significant Of these the most important in cases with extensive damage to muscle seems to be the pressence in the glomerular filtrate of myoglobin liberated from traumatized muscle It was mentioned above that Bywaters and his associates showed that the heme pigment eliminated in the urine in the crush syndrome is myoglobin Since myoglobin has a molecular weight (17 000) much smaller than that of hemoglobin (68 000) it passes through the glomerular filter much more rapidly than hemoglobin— according to Yuile and Clarke[68] about 25 times as fast How heme pigments in the glomerular filtrate may damage the renal tubules will be discussed in more detail in connection with post transfusion nephrosis (p 433) Here it may be mentioned that such injury may result from plugging of tubules by heme casts or by cytotoxic action of heme derivatives entering the cells Blockage of tubules by myoglobin casts can at most be only an accessory factor because in some cases it is absent and in others only a small fraction of the nephrons is affected It is likely that myoglobin derivatives in the glomerular filtrate can exert a toxic action on the tubule cells In rats in which one hind limb was crushed Corcoran and Page[69] found that those which were injected with myoglobin had much more severe degenerative changes in the tubules and more extensive formation of pigment casts than those which were given an equal volume of salt solution That heme derivatives should exert cytotoxic action more readily on tubular cells with nutrition already impaired by ischemia would appear plausible It is indeed also possible that formation of pigment casts is favored by previous ischemic damage to the tubular cells akin to the predisposition to thrombosis by damage to the vessel wall That nephrotoxic substances are formed in traumatized tissues has been suggested but is not supported by convincing evidence

Clinical Picture —In civilian life clinically demonstrable necrotizing nephrosis follows traumatic shock in only an extremely small proportion of the cases In fact the sequence is distinctly a rarity which is doubtless the reason that so little was known of the crush syndrome prior to World War II Most of the few cases in large cities follow automobile accidents How frequently on the contrary the crush syndrome follows battle casualties is shown by Mallory s finding of the lesion in 18 6 per cent of 427 unselected autopsies on battle casualties in Army hospitals in Italy Perhaps the main reason for the difference is that in civilian life in recent

recent years the period of shock following trauma has been greatly abbreviated by prompt administration of blood or plasma and other treatment Whether lesser degrees of renal damage quickly reversed with amelioration of shock follow civilian trauma with greater frequency remains to be studied, but seems very probable in the light of the almost invariable oliguria in shock

Because of the constancy of oliguria in shock the onset of necrotizing nephrosis due to traumatic or surgical shock is rarely suspected in its early stages in civilian practice On very rare occasions on surgical services detection of a smoky brown or red urine which proves to be due to heme pigment (myoglobin or hemoglobin or their met forms) awakens apprehension of severe renal damage Usually however such fear is first aroused when the patient comes out of shock and oliguria persists despite return of blood pressure to normal values or above Or search for the cause of apathy restlessness nausea or vomiting reveals azotemia The oliguria persists or goes on to anuria Correspondingly the nonprotein nitrogen of the blood rises Despite the mounting azotemia for several days the patient may have no symptoms other than those attributable to the injury or may feel well This latent period of several days of relative well being often renders it difficult for the relatives of the patient to appreciate the gravity of the situation In other cases apathy mental torpor or disorientation or nausea and vomiting appear early and the symptoms of the initial trauma and those due to renal insufficiency merge with one another In some cases the patient does not come out of the causative shock which persists with hypotension and renal insufficiency is only one of the factors producing the lethal outcome In others though the cerebral and gastrointestinal symptoms are unremitting from the onset the recovery from shock is evidenced by rise in blood pressure to hypertensive levels and a warm skin

Oliguria is constant In cases seen at the start the specific gravity is high over 1 020 After a day or two the specific gravity falls and is most often around 1 010 despite a urinary volume which may be less than 100 cc In the first days the urine is usually cloudy because of the presence of debris In the cases due to muscle trauma the urine is smoky dirty brown or reddish The discoloration is due to myoglobin for the sediment rarely reveals many red blood cells Bywaters pointed out that the pigment granules and casts may sediment out so completely that the supernatant fluid becomes normal in color and myoglobinuria is overlooked When myoglobin is present it gives a positive benzidine test the latter may be found even when the amount of pigment is not enough to discolor the urine The grossly evident myoglobinuria usually disappears within two or three days At the start while the specific gravity is high the urine is usually very acid the pH may be less than 4 With the development of hyposthenuria the pH rises There is almost always considerable proteinuria due to serum proteins and the urine may boil solid With hyposthenuria the urea concentration in the urine is low despite azotemia Bywaters states that in the crush syndrome the chloride content of the urine tends to be high notwithstanding a low plasma chloride level—like the low concentration of urea an indication of severe tubular damage with diminished ability

to change the composition of the glomerular filtrate in accord with the needs of the organism

The sediment is usually abundant at the start There may be various types of casts and much epithelial debris Red cells are rarely numerous and may be very few The most striking sediment is found in the early days of the crush syndrome It is brown or reddish brown in color and microscopically is seen to contain pigmented casts and granules of myoglobin Casts of various morphologies are seen as a result of conglutination of pigment granules epithelial cells or their debris, and hyaline substance The pigment granules should not be confused with erythrocytes, they disappear after the first days

As a result of the renal insufficiency, azotemia develops and the non protein nitrogen of the blood may reach exorbitant heights The changes in blood chemistry common to all varieties of uremia (p 07) occur These may be altered by special circumstances such as depletion of electrolytes by vomiting or unusual augmentation of the potassium content of the plasma when there is extensive breakdown of muscle according to Bywaters the concentration of potassium in affected muscle falls to less than one-quarter of its normal value in the crush syndrome Renal acidosis is present at the start it may be augmented by lactic and other acids from the traumatized tissues In the early stages the hemoconcentration correlated with the causative shock is revealed by a high hematocrit reading

At the onset the blood pressure is generally low, although exceptionally vasoconstriction fully compensates for oliguria and the arterial tension is maintained After the shock has passed away the blood pressure rises and moderate hypertension is the rule Usually this does not exceed 160/100 mm a considerable hypertension in the face of the debilitated general condition and electrolyte depletion and oligemia that frequently develop Exceptionally the blood pressure rises as high as 200/110 mm Edema is absent unless it is produced by excessive administration of fluid I have not seen retinal lesions from the hypertension

If the oliguria persists or goes on to anuria uremic symptoms (*Chapter 7*) appear within a few days Not rarely azotemia and uremia progress despite increase in urinary volume to such polyuric levels as 3000 or more cc daily In these cases the urine is so dilute that renal insufficiency exists despite the large urinary volume A fatal outcome sometimes from electrolyte depletion may then dash the hopes awakened by the polyuria

The ***prognosis*** is serious in all cases in which the clinical picture definitely indicates necrotizing nephrosis The prognosis was especially grave in the crush syndrome during World War II and in battle wounds About two-thirds of Bywaters cases of crush syndrome succumbed in the first week Lucke estimated the mortality rate in definitely established lower nephron nephrosis at over 90 per cent In necrotizing nephrosis in civilian life the mortality is not nearly as great in my experience less than 50 per cent This is probably largely due to improvement in management of fluid and electrolyte balance Death often occurs suddenly toward the end of the first week In some instances of crush syndrome in which this occurred after cardiac irregularity Bywaters found the electrocardiographic changes

of hyperpotassemia (p 211) the cardiac effect of which is perhaps the immediate cause of the lethal outcome If the patient survives the first week there is a fair chance of recovery although this is by no means sure and the prognosis must be guarded even after polyuria appears

When the patient recovers from necrotizing nephrosis whatever the etiology complete recovery of renal function is usually slow despite the fact that the patient feels entirely well It is generally months before hyposthenuria disappears By measuring urea inulin and PAH clearances Finkenstaedt *et al* [9] demonstrated persistence of impairment of renal function for as long as four and a half years after acute renal failure I have seen no cases of chronic renal disease which demonstrably took origin in necrotizing nephrosis but in view of the frequently protracted impairment of renal function the possibility of such a course of events merits study

The treatment is discussed in Chapter 7

HEMOGLOBINURIC NEPHROSIS

A dreaded result of transfusion of incompatible blood is acute renal insufficiency Since necropsy in the high proportion of cases which are fatal reveals necrotizing nephrosis and hemoglobinuria* plays a fundamental role in the pathogenesis the designation *hemoglobinuric nephrosis* is appropriate The incompatibility may be between major blood groups or Rh incompatibility The consequent hemolysis of the donor s red cells produces hemoglobinemia and hemoglobinuria from which may follow renal insufficiency and/or jaundice Or a hemolytic reaction may result rarely from blood stored improperly or too long In 43 284 transfusions the incidence of hemolytic reactions was 1 8 and the mortality 1 4 per thousand (Kilduffe and DeBakey[77]) Most of these fatalities due to incompatible transfusion are due to renal insufficiency Small as is the incidence of renal failure due to incompatible blood so many transfusions are performed nowadays that hemoglobinuric nephrosis has become a leading

* Hemoglobin a protein of about the same molecular weight as serum albumin (68 000) is excreted by glomerular filtration Hemoglobin behaves like a threshold body Gilligan *et al* [?] found that in normal man it appears in the urine when the plasma concentration exceeds 135 mg per cent although Fox and Ottenberg[?] found the threshold less constant There is good evidence that the tubules take up hemoglobin from the glomerular filtrate by athrocytosis (p 130) and that it appears in the urine only when the amount filtered exceeds the capacity of the tubules for athrocytosis Monke and Yuile found the filtration rate of hemoglobin in the dog about 3 per cent of that of creatinin which is interpreted as indicating that hemoglobin is able to pass through about 3 per cent of the pores of the glomerular membrane (*cf* Yuile [?]) However Smith points out that an alternative explanation is that 3 per cent of the hemoglobin in the plasma is dissociated into smaller molecules to which the glomerular membrane is easily permeable Monke and Yuile find that the tubules of a normal dog can reabsorb by athrocytosis between 2 and 3 mg of hemoglobin per minute This amount is less after hemoglobinuria persists or is soon repeated with corresponding depression of the renal threshold for hemoglobin presumably because of decreased ability of the tubule cells to take up pigment

In man McDonald [?] *et al* find that the permeability of the glomeruli to hemoglobin averages 12 5 per cent of the glomerular permeability to inulin and that tubular reabsorption of hemoglobin averages 17 1 mg per 100 cc of glomerular filtrate

substrate of acute renal insufficiency in this country, in countries where blackwater fever is prevalent it has probably always been the leading cause of acute uremia through the intermediacy of hemoglobinuric nephrosis

Among the other circumstances in which intravascular hemolysis may lead to hemoglobinuric nephrosis are burns, sulfonamide reactions potassium chlorate arsine and other forms of chemical poisoning intoxication by plasmoquine and quinine (taken as an abortifacient) mushroom poisoning favism eclampsia gravidarum, and the intravenous injection of distilled water or hemolysis by hypotonic irrigating fluid during transurethral resection On the other hand Burwell *et al* [78] state that hemoglobinuric nephrosis is rare or has not been observed in the following hemolytic syndromes paroxysmal cold hemoglobinuria, paroxysmal nocturnal hemoglobinuria cold hemoglobinuria due to a high titer of cold agglutinins, and hemolysis of the recipient's cells due to a high titer of isoagglutinins in Group O blood from a universal donor Nor does it occur in march hemoglobinuria or in familial or acquired hemolytic icterus even during crises or in acute hemolytic anemias The reason may be that in these forms of hemolysis the hemoglobin concentration in the plasma does not rise sufficiently high

Pathological Anatomy — The kidneys are enlarged and may weigh over 500 grams The capsule is not adherent The surface and cut section of the cortex are pale gray or mottled and moist The Malpighian bodies are not prominent The medulla is dusky and sometimes brownish radial brown streaks may be seen

The histological picture is dominated by regressive changes in the tubular epithelia culminating in necrosis and by pigmented casts in the lower nephron

The glomeruli show little change There may be protein in Bowman's spaces some of which may be dilated

Most striking when numerous are brick-red or brown granules masses or well formed casts in the lower nephron from the ascending limb of Henle's loop to the collecting tubules The distal segments of many nephrons may be completely occluded by the pigmented masses especially the collecting tubules are apt to be so tightly packed that the lining epithelium appears to be compressed In some cases the casts are numerous in others they are seen in only a small proportion of the tubules The pigmentation is due to heme pigment which gives a positive benzidine reaction The heme derivative has been widely regarded as hematin but casts teased from the tubules of dogs after intravenous injection of hemoglobin by Harrison *et al* [79] proved to be pigmented by methemoglobin and not hematin Heme casts in the lower nephron have been observed as early as one and a half hours after intravenous injection of hemoglobin into dogs (Harrison) and two hours after a hemolytic reaction in man (Ayer and Gauld[80]) In addition to the casts of heme pigment casts of eosinophilic material desquamated epithelial cells and cellular debris are found in all segments of the tubule

The tubular epithelia exhibit regressive changes of various degree Ayer and Gauld observed cloudy swelling and eosinophilic casts in the proximal convoluted tubule as early as three hours after a hemolytic

reaction Droplets of hemoglobin derivatives—having the same color and staining reactions as the pigment in the lumens—may be discernible in the epithelial cells of the proximal and distal tubules *Hemosiderin* recognizable by a positive Berlin blue reaction for free iron appears in the tubule cells The tubular degeneration goes on to more or less wide spread necrosis and desquamation Various segments of the tubule may be implicated Lucke[7] includes hemoglobinuric nephrosis in his concept of *lower nephron nephrosis* It is true that the pigmented casts are found only in the distal portions of the nephron but the regressive changes may also occur in the proximal convoluted tubule This was so in 2 of Bell's[41] 4 cases and in 1 he states that the distal segments were unaffected Dilated tubules are often seen whether these are proximal to obstruction by casts remains to be determined Within a few days regeneration of the tubular epithelium is evident Individual calcified tubules are sometimes seen in the later stages There are varying degrees of intertubular edema and cellular infiltration

The complete functional recovery in cases that survive indicates that tubular regeneration leads to quite complete healing However in a patient who succumbed to homologous serum hepatitis three months after recovery from severe hemoglobinuric nephrosis Burwell *et al* found discrete foci of destroyed nephrons

Pathogenesis — The anatomic findings point to the participation of two pathogenetic factors in the renal failure of hemoglobinuric nephrosis blocking of the tubules by heme casts and necrosis of the tubular epithelium In the effort to unveil the mechanism through which intravascular hemolysis bring about these renal lesions there has been a great deal of clinical and experimental investigation since Ponfick[82] first attempted to reproduce the changes of blackwater fever by injecting heterologous blood into animals and observed pigmented casts in the tubules Subsequent investigators of blackwater fever notably Yorke and Nauss[83] attributed the urinary suppression to mechanical plugging of the tubules by hemoglobin casts On the basis of injection of hemoglobin solutions into rabbits and *in vitro* studies of the precipitation of hemoglobin Baker and Dodds[84] concluded that hemoglobin is precipitated in the tubules only when the urine is acid and has a fairly high concentration of electrolytes These are conditions which are first attained when the urine reaches the lower nephron—*the site of precipitation of heme compounds in hemoglobinuric nephrosis* Similar results were attained by DeGowin *et al*[85] who were able to produce renal insufficiency in dogs by injection of laked erythrocytes only when the urine was acid and not when it was alkaline These experiments accord with clinical observations for heme casts are found only in the lower nephron where the urine is acidified and concentrated However other observers obtained different results De Navasquez[86] and Yuile *et al* could not produce renal damage by injection of crystalline hemoglobin solutions into acidotic dogs though injection of methemoglobin into such animal can ed p ofound depression of renal function Sellard and Minot[88] injected as much as 33 cc of packed red cells laked with distilled water into humans which produced marked hemoglobinuria but there was no

renal damage Gilligan and his associates produced pronounced hemoglobinuria by injection of as much as 16 4 Gm of stroma free hemoglobin into humans without inducing more than transitory proteinuria

It would thus appear that the occurrence of marked hemoglobinuria *per se* does not suffice to produce hemoglobinuric nephrosis Other conditions must also be present Light was cast on these by the experiments of Yuile and his coworkers They first showed that in normal rabbits injection of relatively pure hemoglobin solutions did not damage the kidneys But when the hemoglobin solutions were injected after the kidneys had been damaged by preliminary clamping of the renal artery for fifteen or twenty five minutes or injection of sodium tartrate renal lesions were produced which closely simulated those of human hemoglobinuric nephrosis with regressive changes in the tubular epithelium and heme pigment casts They found that the renal damage was the more pronounced the greater the preliminary tubular injury, the higher the hemoglobinemia and the more acid the urine Flink[89] also found a correlation between the height of the hemoglobinemia and the severity of the renal damage in dogs Hamilton *et al* [90] observed transitory depression of urea clearance after infusion of a 7 per cent hemoglobin solution into dogs this did not occur with plasma

Quite probably a similar constellation of pathogenetic factors operates in clinical hemoglobinuric nephrosis Transfusions are often given to patients in more or less shock who consequently have decreased renal blood flow (p 81) The writer does not recall seeing hemoglobinuric nephrosis follow a transfusion in a patient without some evidence of peripheral circulatory failure During the reaction produced by transfusion of incompatible blood there may also be renal arteriolar constriction and consequent ischemia Mason and Mann[91] and Hesse and Filatov[92] found that intravenous injection of hemoglobin solution is followed by decrease in the volume of the kidney It is true that Harrison *et al* found normal renal blood flow in 2 dogs following injection of methemoglobin in amounts sufficient to produce renal damage but the measurements may not have coincided with the period of shock which is often very transitory The observations of Miller and McDonald [93] to be mentioned below show that in man the injection of hemoglobin solutions can produce renal vasoconstriction Clinical observation (*cf* Bordley[94]) indicates that the more incompatible blood infused the more severe is apt to be the renal damage this is borne out by the observations of Harrison and Flink on the relation of the plasma hemoglobin level to the severity of renal damage following the injection of hemoglobin Early observations that increased urinary acidity favors the formation of heme casts after injection of hemoglobin were mentioned above more recent and carefully controlled studies by Yuile indicate that after injection of hemoglobin solutions into rabbits both heme cast formation and renal functional disturbances are more severe with acid urine The urinary volume may also be an important conditioning factor Harrison found that much lower plasma methemoglobin levels produce renal damage when there is oliguria

Recent experiments by Miller and McDonald[93] show that hemoglobinemia *per se* may produce renal vasoconstriction in man Following the

injection of up to 15 grams of human hemoglobin into individuals free of renal disease they observed rise in arterial pressure fall in renal blood flow (PAH clearance) and glomerular filtration (inulin clearance), rise in filtration fraction and decrease in urine volume

How the hemoglobinemia and hemoglobinuria bring about the necrotizing lesions of the tubular epithelium remains to be elucidated The renal vasoconstriction just described with resultant renal ischemia may well be an important and perhaps an initiating and predominant factor The epithelial necrosis does not result from obstruction of the tubules from heme casts (apart from perhaps the segments in which the tubules are distended and the lining cells appear compressed by pigment masses) for it occurs in unobstructed tubules The hemoglobin is filtered through the glomeruli and some of it or its derivatives is taken up by the tubular epithelia by athrocytosis it leaves its traces behind in the form of stainable iron It is conceivable though unproved that when large amounts of some heme derivatives are taken up by the tubular cells or formed in them they may be cytotoxic especially if the nutrition of the cell is previously impaired by ischemia Harrison *et al* believe that hemoglobin oxidized to methemoglobin in the tubular fluid may act as an oxidant and exert its cytotoxic action through catalysis of the oxidation of sulfhydryl groups they state that there is evidence that the tubular cells are highly susceptible to agents which combine with or oxidize sulfhydryl groups

The relative importance of occluding heme casts and necrosis of the tubular epithelium in the renal insufficiency of hemoglobinuric nephrosis probably varies from case to case and at different stages of the process At most necropsies the proportion of nephrons blocked by casts is so small that this can hardly be the predominant factor in producing renal insufficiency through the intermediacy of internal hydronephrosis * In only 2 of 9 patients succumbing to hemoglobinuric nephrosis did deGowin regard the proportion of tubules blocked by casts as having been enough to constitute a serious factor in the renal failure Tubular epithelial damage appears to be at least most often the predominant element in producing urinary suppression presumably by permitting unselective back-diffusion of the glomerular filtrate (p 412) Indeed as seen above it is likely that the heme casts form only in nephrons with previously damaged epithelia

Clinical Picture —When hemoglobinuric nephrosis results from transfusion of incompatible blood it generally follows an immediate reaction during the transfusion which may have occasioned cessation of the latter Exceptionally the immediate reaction is not evident or is unrecognizably intermingled with the symptoms of the condition for which the transfusion is being given The immediate reaction is more apt to be overlooked when the blood is given to an anesthetized subject this happened in a recent case (*fatal in eleven days*) in which it was thought that mental confusion was due to slow recovery from the anesthetic until jaundice appeared seventeen hours later and hemoglobinuria was looked for and found When the immediate reaction is not observed hemoglobinuria and oliguria call attention to the danger The immediate reaction consists in such

* Harrison *et al* point to the possibility that increased viscosity of the tubular contents in hemoglobinuria may be concerned in obstructing the flow of urine

renal damage. Gilligan and his associates produced pronounced hemoglobinuria by injection of as much as 16.4 Gm. of stroma free hemoglobin into humans without inducing more than transitory proteinuria.

It would thus appear that the occurrence of marked hemoglobinuria *per se* does not suffice to produce hemoglobinuric nephrosis. Other conditions must also be present. Light was cast on these by the experiments of Yuile and his coworkers. They first showed that in normal rabbits injection of relatively pure hemoglobin solutions did not damage the kidneys. But when the hemoglobin solutions were injected after the kidneys had been damaged by preliminary clamping of the renal artery for fifteen or twenty-five minutes or injection of sodium tartrate, renal lesions were produced which closely simulated those of human hemoglobinuric nephrosis with regressive changes in the tubular epithelium and heme pigment casts. They found that the renal damage was the more pronounced the greater the preliminary tubular injury, the higher the hemoglobinemia, and the more acid the urine. Flink[89] also found a correlation between the height of the hemoglobinemia and the severity of the renal damage in dogs. Hamilton *et al.*[90] observed transitory depression of urea clearance after infusion of a 7 per cent hemoglobin solution into dogs; this did not occur with plasma.

Quite probably a similar constellation of pathogenetic factors operates in clinical hemoglobinuric nephrosis. Transfusions are often given to patients in more or less shock who consequently have decreased renal blood flow (p. 81). The writer does not recall seeing hemoglobinuric nephrosis follow a transfusion in a patient without some evidence of peripheral circulatory failure. During the reaction produced by transfusion of incompatible blood there may also be renal arteriolar constriction and consequent ischemia. Mason and Mann[91] and Hesse and Filatov[9] found that intravenous injection of hemoglobin solution is followed by decrease in the volume of the kidney. It is true that Harrison *et al.* found normal renal blood flow in 2 dogs following injection of methemoglobin in amounts sufficient to produce renal damage, but the measurements may not have coincided with the period of shock, which is often very transitory. The observations of Miller and McDonald[93] to be mentioned below show that in man the injection of hemoglobin solutions can produce renal vasoconstriction. Clinical observation (*cf.* Bordley[94]) indicates that the more incompatible blood infused the more severe is apt to be the renal damage; this is borne out by the observations of Harrison and Flink on the relation of the plasma hemoglobin level to the severity of renal damage following the injection of hemoglobin. Early observations that increased urinary acidity favors the formation of heme casts after injection of hemoglobin were mentioned above; more recent and carefully controlled studies by Yuile indicate that after injection of hemoglobin solutions into rabbits both heme cast formation and renal functional disturbances are more severe with acid urine. The urinary volume may also be an important conditioning factor. Harrison found that much lower plasma methemoglobin levels produce renal damage when there is oliguria.

Recent experiments by Miller and McDonald[93] show that hemoglobinemia *per se* may produce renal vasoconstriction in man. Following the

reveals necrotizing nephrosis The glomeruli show little change The segments of the tubule affected apparently vary In 4 instances of pyloric obstruction studied by *Zeman et al* [20] the necrosis involved the proximal convoluted tubule *Contrariwise* in a carefully studied case of necrotizing nephrosis due to pyloric obstruction McLetchie[97] found that the necrosis involved chiefly the ascending limb of Henle s loop and the distal convoluted tubule the resemblance to the crush syndrome was further heightened by the presence of numerous herniations of necrotic tubules into veins (p 426) Especially in the cases due to vomiting with resultant alkalosis there is often secondary tubular calcification (Fig 10) Zeman and his associates produced the same necrotizing nephrosis with calcification in cats by tying off the pylorus The mechanism of the necrotizing nephrosis is doubtless primarily decreased renal blood flow with consequent ischemic damage to the tubular epithelia the decreased renal blood flow is a result of electrolyte depletion and consequent diminution in blood volume Since the nature of the physiological disturbances caused by immoderate vomiting and diarrhea has been better understood and adequate replacement of the lost electrolyte and fluid carried out necrotizing nephrosis of this etiology has become far rarer than it was two decades ago

CHOLEMIC NEPHROSIS (THE HEPATO-RENAL SYNDROME)

Not very rarely when convalescence seems smoothly initiated following an operation on the gall bladder or common duct after an interval of one to six or even more days malaise develops the temperature rises oliguria sets in and may go on to anuria the patient becomes restless and then perhaps delirious or comatose and in a considerable proportion of the cases succumbs with the clinical picture of uremia At first the urine is of high specific gravity but then the impairment of renal function is revealed by hyposthenuria despite persistence or intensification of oliguria and progressive azotemia A similar picture occurs very rarely in acute hepatitis or during acute exacerbations of chronic hepatic disease It develops in a high proportion of patients with acute yellow atrophy In yellow fever Hoffmann[98] found that necrotizing nephrosis with extensive calcification is very common The renal involvement that complicates a high proportion of leptospiral infections and causes most of the deaths is a necrotizing nephrosis (*cf* Stiles *et al* [99]) A similar picture has been observed following traumatic pulpification of the liver (Schutz *et al* [100]) In dogs Helwig and Schutz[101] described renal insufficiency and degenerative changes in the tubular epithelium following experimental pulpification or ischemic necrosis of the liver

Anatomically in the early stages the kidneys may reveal only modest regressive changes in the tubular epithelium This was true in a case at Mount Sinai Hospital reported by Garlock and Klein[102] which did not succumb until the twelfth day Most often however severe regressive changes going on to focal necrosis of the tubular cells soon appear with little change in the glomeruli The tubular epithelium contains granules of bile pigment (according to Allen[103] this involves only the proximal nephron down to Henle s loop) and there are bile stained casts in the lower

manifestations as restlessness, weakness, confusion, sweating, chills high fever, vomiting, pains in the back, tingling, thoracic oppression, cyanosis, dyspnea, fall in blood pressure, collapse, and urticaria These immediate symptoms apart from very rare instances of quick death, generally subside within a matter of hours Not every patient who has such an immediate reaction and recovers, develops clinically evident hemoglobinuric nephrosis Especially if the reaction is quickly detected and the transfusion stopped before much blood is given, urinary suppression is unlikely While severe hemoglobinuric nephrosis has been observed with transfusion of less than 100 cc of incompatible blood, the incidence increases with the size of the transfusion Jaundice appears in a high proportion of the patients who are to develop urinary suppression but not in all

After subsidence of the immediate reaction the patient may feel deceptively well until the renal insufficiency brings about uremic symptoms However the true state of affairs is indicated by the oliguria which may go on to anuria In the first days, the urine is red or brown from hemoglobin or methemoglobin and heme-pigmented granules and casts are present These quickly lessen and disappear in a few days as a result of clearing of the hemoglobinemia, which occurs rapidly The specific gravity of the small amount of urine passed is fixed in the vicinity of 1 010 and the urea concentration is low Correspondingly there is mounting azotemia The clinical picture of acute renal insufficiency (Chapter 7) develops The blood pressure generally though not always rises but marked hypertension is very rare Retinal lesions are absent Edema does not develop other than terminal pulmonary edema unless excessive fluids are forced or there is heart failure At any time no matter how desperate the situation and even after the patient is in uremic coma the urinary volume may increase and rapid improvement set in This may occur as late as the end of the second week Goldring and Graef[95] observed advent of diuresis and recovery after sixteen days Sometimes the onset of diuresis occurs too late to save the patient who succumbs despite a urinary volume of over 3000 cc which unfortunately is very dilute The mortality is high Formerly it was probably over 50 per cent of the cases in which the damage to renal function was severe enough to produce pronounced azotemia But since fluid and electrolyte balance have been better controlled the mortality has not been as high

The treatment is discussed in Chapter 7

NECROTIZING NEPHROSIS DUE TO VOMITING AND DIARRHEA

With severe vomiting azotemia often develops The same frequently occurs in the diarrheal diseases of infancy it is rare except in the tropics in severe diarrhea in adults According to the descriptions by Fraenkel and Simmonds[96] of the anatomical findings in the Hamburg cholera epidemic, severe necrotizing nephrosis is present in most fatal cases of cholera In some instances of pyloric or intestinal obstruction as well as in intractable vomiting in peritonitis renal insufficiency dominates the clinical picture and the patient becomes uremic In such cases necropsy

protein content of the urine Circulatory disturbances may be concerned Smith[108] and Bradley and his coworkers[109] showed that injection of a pyrogen even if rise in temperature is prevented by aminopyrine produces a remarkable hyperemia of the kidney which is sometimes though not always preceded by brief renal ischemia Such circulatory perturbations may be damaging to the renal epithelium Another and perhaps more important factor is injury to the renal cells by circulating toxic substances, for similar renal lesions and proteinuria occur in various afebrile toxemias and chemical poisoning

As a rule, proteinuria first appears after several days of fever, though it may come on sooner and disappears rather quickly after the temperature has declined The quantity of protein is rarely great in fact it is usually less than 0 1 per cent. But there are unusual instances in which febrile proteinuria is of high degree as much as 1 per cent of protein being present in the urine Albumoses may accompany the albumin and have been observed even in the absence of the latter (Krehl and Matthes[110]) Small numbers of hyaline casts are often present and in some cases there are scattered granular casts Any considerable number of blood or epithelial cells points to the existence of a more severe lesion than the cloudy swelling and slight fatty change of what is here termed *febrile nephrosis* Renal function is not significantly impaired the urine presenting the usual febrile characteristics of small daily volume deep color generally abundant sediment high specific gravity and low chloride content Edema and hypertension are absent

The slight renal changes which result in febrile proteinuria exert no influence on the course of the primary disease They offer no diagnostic or prognostic aid and call for no modification in the dietetic or other treatment

Larval Nephrosis in Anemia —Usually slight proteinuria and cylindruria are common in severe anemia If the hemoglobin is very low functional impairment of the tubular cells is shown by hyposthenuria In pernicious anemia Christian[111] and Major long ago showed that when the patient is severely anemic there may be marked impairment of concentrating power The defective renal function in this disease is probably due to poor oxygenation of the kidney cells by the anemic blood the increase in renal blood flow does not compensate for the diminished oxygen carrying capacity of the blood Tubular reabsorption is an active process in which work is performed and consequently oxygen required On the other hand Stieglitz[112] believes that the function of the tubular cells may be impaired by the siderosis which is constantly present That this is not the main cause is shown by the occurrence of hyposthenuria in secondary anemias where there is no siderosis and by the fact that the concentrating ability of the kidney is quickly affected by changes in the hemoglobin content of the blood According to Essen and Porges[114] impairment of renal function is not yet present when the hemoglobin has dropped to 50 per cent but is very evident at 30 per cent One often sees quick restoration of concentrating ability when the anemia is overcome by appropriate treatment Fouts and Helmer[11] found that the induction of a remission by liver treatment is accompanied by a rise in urea clearance

nephron The functional significance of the deposition of bile pigment is probably not great Brown or green amorphous or crystalline spherules of undertermined composition are often found in the tubules (Allen)

How the liver disease leads to the renal damage remains to be elucidated As mentioned above, in cases succumbing early comparatively little morphological damage is seen in the kidneys, the necrotizing nephrosis develops later The patients often display pronounced evidence of peripheral circulatory failure doubtless at least largely a result of diminution in circulating blood volume It therefore appears likely that decreased renal blood flow plays an important part in the renal failure (prerenal azotemia) As yet completely obscure metabolic derangements resulting from the liver damage may underlie the hypovolemia and circulatory failure, Page's[104] finding that hepatectomized animals lose their vascular reactivity may be relevant in this connection Such factors as surgical shock and vomiting undoubtedly often also contribute and may dominate But in some instances of the "hepato renal syndrome," these banal causes of renal failure do not seem to operate

LARVAL NEPHROSES

Proteinuria may occur in the course of febrile diseases afebrile toxemias severe anemia marked alkalosis or acidosis and various other states in which there is reason to assume abnormalities in the composition of the blood The proteinuria is usually slight and does not deplete the plasma proteins Anatomical investigation in cases of this nature may show little that is definitely abnormal or there may be cloudy swelling hyaline droplet degeneration or lipidal change in the epithelial cells of the kidneys In addition to these regressive changes in the renal epithelium there may also be storage in these cells of substances such as glycogen in diabetes mellitus and iron in pernicious anemia These proteinurias document the mildest forms of nephrosis for which reason they are here termed larval

Febrile Proteinuria (Febrile Nephrosis) — The occurrence of proteinuria in fevers was first described by Solon,[105] and was termed febrile albuminuria by Gerhardt[106] Proteinuria may occur in almost any febrile state but is most common when the fever is very high and protracted

Anatomically cloudy swelling of the epithelium particularly of the convoluted tubules is found Not uncommonly there is also lipidal change of varying degree though rarely marked The proteinuria has generally been correlated with these changes in the tubules It should be mentioned however that similar cloudy swelling and lipidal change may be found when there was no proteinuria during life Presumably the actual proteinuria is due to injury to the epithelium covering the glomerular loops, about which we can tell little from the microscopic examination

It would appear that pyrexia *per se* is one though probably not the most important factor in the causation of febrile proteinuria This is indicated by the finding of Welty[107] that 77 5 per cent of 40 patients with healthy kidneys whose body temperature was elevated to between 105° and 106° F for four to six hours by the Kettering hypertherm had an increase in the

protein content of the urine Circulatory disturbances may be concerned Smith[108] and Bradley and his coworkers[109] showed that injection of a pyrogen even if rise in temperature is prevented by amidopyrine produces a remarkable hyperemia of the kidney which is sometimes though not always preceded by brief renal ischemia Such circulatory perturbations may be damaging to the renal epithelium Another and perhaps more important factor is injury to the renal cells by circulating toxic substances for similar renal lesions and proteinuria occur in various afebrile toxemias and chemical poisoning

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ADDENDUM: RENAL INVOLVEMENT IN MULTIPLE MYELOMA

A remarkable and specific renal lesion occurs in multiple myeloma. In fact in somewhere between a half and a third of the cases renal insufficiency with consequent uremia is the dominant immediate cause of the fatal outcome (*cf.* Adams *et al.*[116]). Occasionally, myeloma is discovered in seeking for the cause of initially obscure renal insufficiency or proteinuria. In most instances, the only clinical manifestations of the specific renal lesions of multiple myeloma consist in proteinuria, hyposthenuria, azotemia and symptoms of uremia. Clearance studies by Armstrong[117] revealed that both glomerular filtration and tubular excretory capacity are impaired (blocking of a tubule would of course abolish filtration in the appertaining glomerulus). Edema is most often absent until the terminal stage, when it is difficult to separate the roles of proteinuria and undernutrition in its production. Hypertension occurs in so small a proportion of these usually elderly patients that it may be coincidental. I do not recall hypertensive retinopathy or encephalopathy. Study of the urine in patients with azotemia reveals hyposthenuria. But the proteinuria is very variable in amount and composition. Either or both Bence-Jones proteins and serum albumin may be demonstrable by the usual clinical methods. Magnus-Levy,[118] who has studied the renal manifestations of multiple myeloma intensively, finds that massive proteinuria is largely due to Bence-Jones proteins. He states that Bence-Jones proteins have failed of detection because under certain conditons, especially when present in large quantity they may be insoluble in boiling urine. In some cases which succumb to renal insufficiency nothing more than a faint trace of protein may be demonstrable in the urine during a period of observation of weeks or months. When urethane inhibits plasma cell growth Bence-Jones proteins diminish in or disappear from the urine (Rundles *et al.*[119]). Armstrong found no relation between the proteinuria and the degree of renal damage.

The renal lesions of multiple myeloma are characterized by the presence of casts in the lower nephron and tubular atrophy terminating in disappearance of the nephron with replacement fibrosis. Grossly the kidney is usually rather pale with a smooth surface. Most often it does not differ much from the usual size, but it may be a little enlarged or definitely contracted. Microscopically in the cases which have succumbed with renal insufficiency the most striking feature is usually the presence of great numbers of large, occlusive casts in the collecting tubules and sometimes the distal convoluted tubules; they may also be found in the loop of Henle. The casts are dense and stain bright pink in hematoxylin-eosin preparations; they may be laminated. The casts are often surrounded by cells which have been regarded as foreign body giant cells but that Allen[1] interprets as syncytia of fused tubular epithelia. Sometimes masses of crystals are seen in the tubules. The crystals are doubtless Bence-Jones proteins and there is every reason to believe, though this has not been proved, that the casts contain these bodies. The tubules exhibit various stages of regressive change and atrophy going on to complete disappearance. The distegration of the tubular cells calls forth a highly cellular

reaction which goes on to fibrosis In most cases the surviving glomeruli are not strikingly altered individual instances of extensive hyaline plugging of glomerular loops have been reported (Bell[11] Loord[122]) Metastatic calcification of the tubules and casts may occur, doubtless a result of the proteolytic process

The evidence indicates strongly that the renal lesions of multiple myeloma result from obstruction of the tubules by casts Thannhauser and Krauss[123] seem to have been the first to realize that the renal lesions of multiple myeloma originate in destruction of the tubules, they regarded the condition as a nephrotic contracted kidney From study of the sections of their case Bohnenkamp[124] pointed out that the tubular destruction takes origin in obstruction of the lumens by casts The findings all



FIG 13 —Section of kidney in multiple myeloma with Bence-Jones proteinuria The tubules are obstructed by casts of Bence-Jones protein around which foreign body giant cells have formed

accord with the conception although it has not been proved that the casts take origin in the precipitation of Bence-Jones proteins in the distal tubule after the tubular fluid has been concentrated by reabsorption of water alterations in the electrolyte constellation of the fluid occurring during tubular processing may also be concerned The Bence-Jones proteins(they apparently are multiple all secreted by the myeloma cells) are of relatively small molecular size—molecular weight about 28 000—and pass through the glomerular filter into the tubular fluid It is to be presumed that up to a certain concentration the Bence-Jones proteins are reabsorbed by the tubular cells by athrocytosis (p 130) but if the concentration is higher the proteins remain in the tubular fluid either to be eliminated in the urine or precipitated as casts when enough water is

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reabsorbed The results of injection of Bence-Jones proteins into animals have been conflicting McMahon and Magnus Levy[15] observed tubular changes but Forbus and associates[16] obtained no characteristic lesions and were unable to reproduce the casts without previously induced hydronephrosis There seems no reason to believe that Bence-Jones proteins are specifically nephrotoxic the renal damage results from obstruction of the tubules and perhaps—though this is purely hypothetical—from "choking" of tubular cells which have reabsorbed large amounts of the proteins

The uremic picture resulting from renal insufficiency in multiple myeloma is fundamentally the same as that in other forms of renal damage Often deterioration is slow and an azotemic patient may get along for a year or two usually with numerous transfusions The anemia often dominates the symptomatology and presumably is due to both the bone marrow damage and the renal insufficiency

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Chapter

16

CHRONIC NEPHROSIS

CHRONIC nephrosis* is characterized clinically by copious albuminuria and edema, chemically by striking changes in the proteins and lipids of the plasma, and anatomically by non-inflammatory lesions in the kidney. Perhaps the most remarkable feature of chronic nephrosis, and one which has attracted to it interest out of proportion to its frequency, is that the symptomatology seems to consist almost purely in the consequences of hypalbuminemia due to massive albuminuria. Together with certain types of glomerulonephritis and doubtless diabetic glomerulosclerosis, chronic nephrosis constituted the chronic parenchymatous nephritis of older clinicians and the large white kidney of pathological anatomists.

What is here termed chronic nephrosis is widely known by Munk's[1] designation *lipoid nephrosis*. It will be seen below, however, that the available evidence indicates that the lipemia and consequent deposition of lipid in the tubular cells are secondary to the proteinuria. The designation chronic nephrosis is used because it is noncommittal regarding the (still unknown) nature of the disease; it merely expresses the defining characteristics of the renal lesions, *i.e.*, that they are chronic and non-inflammatory.

The separation of chronic nephrosis from glomerulonephritis and its recognition as a distinct clinical and anatomical entity was accomplished by several investigators in the second decade of this century. In 1913 Munk[1] published a series of cases of supposedly syphilitic etiology which were marked by edema, great proteinuria and the presence of doubly refractile lipoids in the urine. He emphasized particularly the finding of anisotropic lipoids in the urine, which he considered as demonstrating the degenerative nature of the renal lesions (actually they are also found in glomerulonephritis). Immediately following Munk's publication there appeared the classical monograph of Volhard and Fahr,[2] in which the clinical and anatomical picture of chronic nephrosis (or genuine nephrosis, as they called it) was exhaustively described. Soon after, Epstein[3] published his pioneer chemical and clinical investigations, dating back many years, which correlated for the first time the characteristic changes in the colloids of the plasma, related the edema to the hypoproteinemia, and introduced the high protein diet.

* Chronic nephrosis designates a *disease entity* (perhaps entities). In accord with now widespread usage, the term *nephrotic syndrome* serves to designate the *clinical picture* resulting from depletion of plasma albumin by albuminuria, whatever the cause of the latter; it includes albuminuria, nephrotic edema, hypalbuminemia, inversion of the albumin/globulin ratio and lipemia.

The introduction of the concept of chronic nephrosis as an entity distinct from glomerulonephritis inaugurated a controversy which has not yet fully subsided Many cases with necropsy findings showing the absence of inflammatory lesions have been published Nevertheless, unanimity of opinion as to the *nature* of the pathological process underlying the clinical manifestations and anatomical lesions has by no means been attained Some investigators regard the disease as primarily acute glomerulonephritis which has healed so as to leave little or no evidence of the original inflammatory processes but only secondary degenerative changes Others, and they are now in the decided majority, admit the primarily non inflammatory nature of the lesions but differ as to whether the condition starts as a

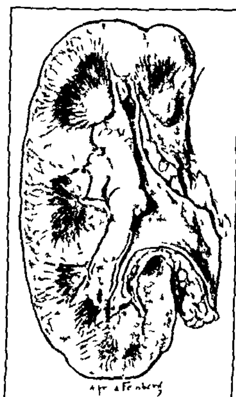


Fig 14 —Kidney in chronic nephrosis occurring about six months after syphilitic infection Note the prominent radial striation of the cortex due to the light streaks of lipoid deposit (yellow in the specimen)

kidney disease or if it is not initially a disorder of metabolism one of the results of which is the renal lesion The writer feels strongly that chronic nephrosis is a disease entity (or entities) *sui generis* distinct from glomerulonephritis *The evidence for this view is summarized below*

THE PATHOLOGICAL ANATOMY OF CHRONIC NEPHROSIS

Chronic nephrosis has been regarded as a rare finding at necropsy some physicians of large experience claim never to have witnessed an unequivocal case Nevertheless a considerable number of necropsies on

cases of chronic nephrosis has been reported by Volhard and Fahr, Munk Murphy and Warfield[4] Loewenthal[5] Holt and Howland[6] Major[7] Bock and Mayer[8] McElroy[9] Bell[10] (see p 463), Wolbach and Blackfan[11] Shapiro,[12] Ehrich[13] Kantrowitz and Klemperer,[14] Bennet[15] Hitzrot and Read[16] Blackman[17] Terbrueggen[18] Murphy and associates[19] Addis and Oliver,[20] and others I saw 6 such necropsies in a period of five years 2 of the cases are reported in the paper of Kantrowitz and Klemperer A high proportion of the reported necropsies have been in children Bell[10] found that 18 of 24 children under ten years of age with nephritis actually exhibited lipoid nephrosis at autopsy In recent years necropsies revealing chronic nephrosis in patients who did not succumb to renal insufficiency have become much rarer presumably because some of those who formerly succumbed pneumococcus peritonitis and other infections are now saved by antibiotics The syphilitic cases have practically disappeared On the other hand because of the persistent dogma that glomerular hyalinization in the absence of arteriolar sclerosis bespeaks glomerulonephritis many cases of chronic nephrosis going on to glomerular hyalinization and uremia are doubtless histologically diagnosed as glomerulonephritis much as was formerly the case with diabetic glomerulosclerosis The writer has no doubt that he made this mistake many times in the past

The kidney is normal in size or more often moderately enlarged the consistency is soft The capsule strips readily from the smooth surface which is usually pale and grayish yellow in color variegated here and there by spots and streaks of brighter yellow On section the cortex is seen to be broadened and clearly separated from the darker medulla The cortical substance feels and looks greasy Here also the yellow areas of intense fatty change stand out Or radially arranged yellowish streaks may alternate with red areas

Histologically changes are seen in both the glomeruli and the tubules In the type of case in which chronic nephrosis was first differentiated—i e massive proteinuria and edema without renal insufficiency—the changes in the glomeruli are not conspicuous while there is very striking deposition of lipid in the tubular cells Attention was thus focused on the tubules and the glomeruli were often reported as histologically normal the process was sometimes spoken of as tubular nephritis Actually the relatively inconspicuous changes in the glomeruli are doubtless of more importance than the deposition of lipid in the tubular epithelia which probably represents athrocytosis from the lipid rich glomerular filtrate and at least often has little effect on the function or vitality of the cell With further progress of the disease especially in adults in whom hypertension and renal insufficiency have developed *glomerular* hyalinization and tubular atrophy become *more* prominent These are the cases which as indicated above have *often* been regarded as chronic glomerulonephritis and thus not included in the rubric of nephrosis

The Glomeruli —The Malpighian bodies were originally *considered* to show practically no morphological changes *in chronic* nephrosis Later Fahr[2] and Munk[21] described glomerular lesions of varying severity knowledge of these glomerular lesions which *are more* important than the often blatant lipoid deposition in the tubular cells is largely due to the

investigations of Bell[4] with the Mallory-Heidenhain azo-carmine stain which brings out the basement membrane clearly In the cases mostly in children, which have a clinical picture of proteinuria and edema in the absence of hypertension and renal insufficiency, the glomerular changes are usually slight and may be hardly demonstrable Most important is that the large majority of the glomerular capillaries remain widely patent Such lesions as exist are degenerative the endothelial and epithelial proliferation that constitutes the hallmark of glomerulonephritis is absent or minimal and focal A varying portion of the glomeruli exhibits swelling and lipidosis of the walls of the loops and the visceral and parietal layers

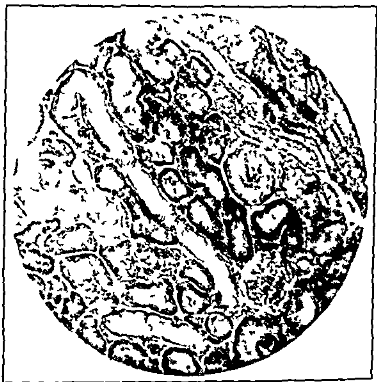


FIG 15 —Frozen section of kidney in chronic nephrosis stained with Sudan and hematoxylin The lipid in the tubular cells which has been stained by the Sudan appears black

of Bowman's capsule Bell and Kantrowitz and Klemperer found the lipid deposited in the endothelial as well as the epithelial cells the endothelial cells which contain lipid may be greatly swollen and more prominent than normally thus simulating proliferation The lipid deposited in the endothelial and epithelial cells of the glomeruli is partly doubly refractile and very small in amount compared to the amount of cholesterol esters in the tubular cells Bowman's capsule usually contains coagulated protein Even in these cases without renal insufficiency or hypertension there may be some degree of thickening of the basement membrane of the capillary loops In other cases as Bell[4] showed the basement membranes are diffusely thickened to such an extent as notably to narrow the capillary

lumens * The advance of this process leads to complete hyaline obliteration of the affected loop and the termination is the destruction of a varying proportion of the glomeruli George Fahr has published beautiful examples of the evolution of hypertension and renal insufficiency in chronic nephrosis *pari passu* with glomerular obliteration by thickening of the capillary basement membrane Bell finds that the thickening of the basement membrane is related to age He did not observe diffuse thickening in any of his 18 cases of lipoid nephrosis under eighteen years of age (3 showed thickening in a few glomeruli) while of 37 cases over twelve years of age 31 had diffuse and 5 focal thickening The histological appearance in these cases of chronic nephrosis with glomerular hyalinization closely simulates that of glomerulonephritis and they have doubtless generally been classified as the latter disease The most important differential point is the absence of cellular proliferation in chronic nephrosis but there are many cases in which certain differentiation is not feasible

The Tubules — As already mentioned in cases succumbing to infection in the absence of hypertension or renal insufficiency the microscopic picture has for its most striking feature degenerative changes in the renal epithelia In most instances these lesions are very well marked but there are also cases in which the microscopic appearance is not that of a change of great severity The proximal convoluted tubules are involved to the highest degree the distal convoluted tubules and Henle's loops to a less extent while the collecting tubules are but little affected Many of the tubules are dilated and lined by flattened cells while in others the swelling of the epithelial cells narrows the lumen greatly There is a striking deposition of fat and lipoid in the epithelial cells in some places so great as practically to fill the entire cell body with Sudan staining substance and give it a vacuolated appearance in sections which have been passed through fat solvents Under the polarizing microscope it is seen that most of the lipoids are doubly refractile (cholesterol esters) However in the case of a child on the service of Dr Herman Schwarz in which hypercholesteremia was absent during life anisotropic lipoids could not be demonstrated in the kidneys postmortem Such absence of doubly refractile lipoid in the tubular cells is apparently very exceptional at least I do not recall seeing or reading of any other instance of chronic nephrosis in which they were absent Leiter points out that the presence of anisotropic lipoids in the renal epithelia is very characteristic of the nephrotic syndrome being rarely seen in other conditions although isotropic fatty change occurs under a variety of circumstances There may be also considerable hyaline-droplet and vacuolar degeneration The nuclei of most of the cells are intact but others have undergone necrobiosis and their nuclei no longer take the stain In places the injured epithelial cells have been desquamated into the lumen where they lie with casts granular material and cellular detritus

The degenerated tubular cells are replaced by regeneration Fahr describes the process of regeneration as akin to that found in mercurial necrosis starting with the formation of flat almost endothelium-like cells under the degenerated elements

* Because of the importance of the thickening of the capillary basement membrane Bell speaks of these cases here termed chronic nephrosis as membranous glomerulonephritis

In the cases with extensive glomerular hyalinization and obliteration, there is tubular atrophy which may be widespread This is presumably secondary to the glomerular lesions decreased blood supply and disuse may be concerned

In cases of considerable standing there is irregular proliferation of interstitial connective tissue between the tubules This is entirely a secondary change, apparently a reaction to the parenchymatous lesions and where there has been tubular atrophy a "replacement fibrosis" for destroyed tubules The presence in the interstitium of nests and cords of cells laden with doubly refractile lipoid is very striking in some cases In sections which have passed through alcohol the lipoid has been dissolved out so that the cells have a clear cytoplasm like that of xanthoma

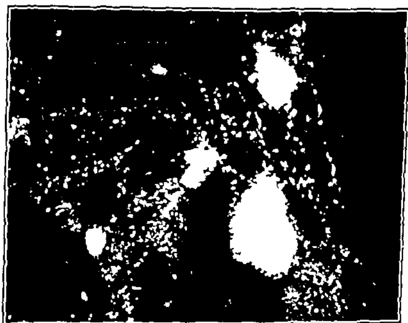


Fig 16 —Section of kidney in chronic nephrosis (same case as Fig 14) viewed through polarizing microscope with crossed Nicol prisms Only the doubly refractile lipoid is visible being brilliantly luminous in an otherwise dark field It is present in large interstitial masses as well as in the tubular cells

cells ("pseudoxanthoma cells") There can be little doubt that these are cells which have taken up the lipoid freed by the disintegration of degenerated epithelia The origin of these lipoid phagocytes is disputed Some authors believe them to be phagocytic wandering cells while others regard them as endothelial cells of lymph capillaries The frequently linear arrangement of the cells would seem to speak for the latter view

The vessels of the kidney are usually unaffected However there may be atherosclerotic changes as a part of the widespread atherosclerosis which Loewenthal[3] found in chronic nephrosis in young individuals I have repeatedly seen atheroma much beyond the expected for the age at necropsy in nephrotic children it is possible that it is correlated with the hypercholesteremia Rarely thrombi form over the atheromatous

areas perhaps favored by the high fibrinogen content of the blood In a boy aged eleven years studied by Schwarz and Kohn [6] whom I also saw there was widespread atherosclerosis and thrombosis of the bronchial and cerebral arteries the latter of which produced hemiplegia and proved fatal A nephrotic child with thrombosis of the aorta and another with an antemortem clot in the pulmonary artery were observed by Block *et al* [9] Remarkably enough they did not detect atheromatosis in these cases so the arterial thrombosis may have been due solely to the changes in the blood

As the end stage of chronic nephrosis Volhard and Fahr have described a *nephrotic contracted kidney* According to their description the nephrotic contracted kidney is small and irregularly granular the granules being yellow in color Fahr and Munk originally believed that the contraction in these cases results only from primary tubular degeneration and atrophy Later however Fahr attributed greater significance to the degenerative changes in the glomeruli as the primary cause of the contraction in analogy to what occurs in glomerulonephritis and the amyloid contracted kidney Others have doubted the existence of a true nephrotic contracted kidney apart from the amyloid contracted kidney Apparently chronic nephrosis can be present for a long time without the development of a contracted kidney for contraction was absent in Ehrich's[17] case of eighteen years duration The least equivocal cases of nephrotic contracted kidney seem to be those of syphilitic origin described by Munk [1] Shapiro[12] also published a case of nephrotic contracted kidney in a syphilitic I have not seen any example of nephrotic contracted kidney

THE ETIOLOGY OF CHRONIC NEPHROSES

Occurrence —It is difficult to estimate the frequency of chronic nephrosis The disease has generally been regarded as very rare among adults some experienced clinicians and pathologists claim never to have seen an unequivocal example Many of the published cases are undoubtedly chronic glomerulonephritis Contrariwise the general assumption that glomerular hyalinization is always due to either arteriolosclerosis or glomerulonephritis (in recent years diabetic glomerulosclerosis has also been recognized) has led to the diagnosis of some perhaps many instances of chronic nephrosis as glomerulonephritis Over a period of many years at Mount Sinai Hospital several cases of chronic nephrosis were seen annually Rosenberg[30] observed 39 examples of lipoid nephrosis among 420 acute nephritides i e about 10 per cent In the opinion of the writer chronic nephrosis is not as rare among adults especially after the age of fifty as has generally been thought Many if not most of the instances in which a nephrotic syndrome sets in insidiously in the elderly are cases of chronic nephrosis and not glomerulonephritis they have been regarded as the latter because glomerular hyalinization is found at necropsy Chronic nephrosis is not rare in children especially under the age of five I see many cases annually in private practice Large series of pediatric cases were long ago published by Holt and Howland [8] Marriott [31] Clausen [32] Schwarz and Kohn [33] and Wolbach and Blackfan [34] Some of these cases doubtless

were chronic glomerulonephritis in the nephrotic phase, but others were chronic nephrosis In 6 necropsies on young children with a nephrotic syndrome Heymann and Startzmann[34] found 3 without any inflammatory lesions in the kidney, in the other 3 the inflammatory changes were interstitial and pyelonephritic

Age Incidence and Predisposing Factors —Chronic nephrosis is seen most often in childhood especially before the age of five years However cases are also seen in all subsequent decades As mentioned above the writer believes that many nephrotic syndromes in the elderly are actually due to chronic nephrosis and not glomerulonephritis as they have been almost universally regarded

Apart from youth little or nothing is known of any factors predisposing to chronic nephrosis Knauer[35] believes that the disease occurs predominantly in pasty children with evidence of the exudative diathesis Volhard[36] who observed cases in two brothers thinks that there may be a familial predisposition This author also saw several cases that followed working in the wet There has been no evidence of the significance of any of these factors in my experience

Causation —Some cases of chronic nephrosis are manifestly the result of an infection In others—in my experience by far the larger part—the etiology remains entirely in the dark for which reason they have been termed genuine or cryptogenic nephroses Older etiologic statistics are typified by Rosenberg's 39 cases of chronic nephrosis of which 16 were syphilitic 7 followed diphtheria 2 dysentery and 1 accompanied pulmonary tuberculosis Nowadays in large segments of the population syphilis and diphtheria have practically vanished as etiologic factors In the cases of chronic nephrosis in adults that I have seen the etiology has almost always been obscure edema appeared or proteinuria was discovered incidentally and careful questioning elicited no antecedent infection In the much more frequent cases in young children the onset sometimes follows an upper respiratory infection such infections had occurred one to four weeks before the onset of edema in about 35 per cent of Heymann and Alpern's[37] patients But the nature of the connection if any between these infections and nephrosis remains to be elucidated I have been impressed by the contrast between the very high incidence of respiratory infection preceding acute glomerulonephritis and the much lesser frequency with which a history of such infection is elicited in nephrosis

Syphilitic Nephrosis —The frequent occurrence of proteinuria in syphilitics was known even before the time of Bright but was considered by Blackall[38] and other physicians of the time as always due to mercury used in treatment But Rayer[39] maintained that the germ of syphilis can cause renal lesions Since his time the picture of what is here termed syphilitic nephrosis has been well known under the name of acute syphilitic nephritis The view that syphilitic nephrosis is due to mercury has been completely disproved by the observation of cases in which the patient had never been given mercury and improved directly after the administration of the drug Moreover even the most severe mercurial nephrosis is marked by little or no edema which is the outstanding clinical characteristic of typical syphilitic nephrosis That acute syphilitic nephritis is a typical lipoid nephro-

sis* has been demonstrated especially by Munk though Dieulafoy had previously observed the exclusively tubular localization of the lesions. Later instances of syphilitic nephrosis were published by Herrmann and Marc, Baker, Patton and Corlette, Moore and others. In a patient at Mount Sinai Hospital who developed a classical nephrotic syndrome during secondary lues and succumbed to erysipelas due to the use of Southey tubes necropsy revealed only anisotropic lipoidosis of the tubules.

Syphilitic nephrosis occurs almost exclusively during the secondary period of lues, the stage of the roseola and mucous patches. Dieulafoy gives the following dates of onset in 17 cases of syphilitic nephrosis: In 2 cases eight months after infection, in 2 six months, in 2 four months, in 5 three months, in 5 two months. Syphilitic nephrosis has been observed within a month of the primary lesion. It is thus one of the results of the generalization of the infection and is almost invariably accompanied by other manifestations such as roseola, mucous patches, adenitis, etc. However, Vorpahl, Schittenhelm and others have observed cases occurring years after the primary lesion. In fact, Schittenhelm's patient suffered from two attacks of typical luetic nephrosis, the first four years and the second six years after the infection, on each occasion improving with antiluetic treatment.

Syphilitic nephrosis severe enough for the edema to be notable became very rare in this country after the introduction of the arsenicals and has practically disappeared since penicillin has come into use. However, the same is true of other secondary and tertiary manifestations of lues well known to Jonathan Hutchinson's generation. Mild cases marked by only proteinuria are apparently more common. Peterson found renal involvement in 3.8 per cent of cases of secondary syphilis. According to Munk, syphilitic nephrosis is more common in females.

Hoffmann, Vorpahl and others claim to have found spirochetes in the urine of patients with syphilitic nephrosis. Nevertheless, even if these spirochetes were actually the organisms of syphilis, the non-specific nature of the renal lesions renders it probable that the nephrosis is not due to the direct invasion of the kidneys by the spirochetes.

Other Infections.—Chronic nephrosis may also follow infections other than syphilis, though our knowledge of the causation of most such cases is very meager. The relation of chronic nephrosis to upper respiratory infections has been discussed above.

* Lipoid nephrosis is not the only renal lesion that results from syphilis. Rich has described a specific syphilitic nephritis. He observed this renal lesion in 13 of 200 necropsies on syphilitics. Grossly, grayish yellow flecks are seen in the cortex and the process may go on to scarring with irregularity of the surface. The lesions consist in interstitial foci of lymphocytes, plasma cells and other mononuclear cells which may compress tubules. Macrophages laden with cholesterol may be seen in the adjacent tubules and there may be interstitial lipid deposits. The process seems to be a true interstitial nephritis of syphilitic etiology. Rich did not demonstrate spirochetes in the lesion. Whether the lesions are ever sufficiently extensive to be of functional and clinical significance seems doubtful. Bauer published a case in which this may have been true. On rare occasions acute glomerulonephritis with bloody urine has been described as complicating secondary or congenital lues (I have not seen this). Rich explains such cases as due to secondary infections in ulcerative lesions of the pharynx and thus not really syphilitic. Gumma of the kidney is a great rarity.

In extremely rare instances, diphtheria is complicated by chronic nephrosis

Pneumococcus infections have also been considered as a cause of chronic nephrosis Volhard noted that of 7 cases of chronic nephrosis, 4 died of pneumococcus peritonitis Similar observations have been made by Holt and Howland, Bock and Mayer Stolz[81] McElroy, Schwarz and Kohn, and others A number of such cases have occurred at Mount Sinai Hospital Pneumococci have also been cultivated from other lesions (see p 478) and from the blood by Schwarz and Kohn McElroy and others Blackman[17] has published a series of 10 cases of what he regards as pneumococcal lipoid nephrosis and produced renal changes with edema in rabbits by the injection of pneumococcal toxin Nevertheless the question of the relationship of pneumococcus infections to chronic nephrosis is by no means settled While some cases may be of pneumococcal origin, it seems likely that most pneumococcal infections in chronic nephrosis are secondary invasions, due to the greatly decreased resistance to infection which most patients with chronic nephrosis exhibit For while infections with pneumococci are the most common in chronic nephrosis other organisms may also be responsible Schwarz and Kohn have repeatedly observed hemolytic streptococci to be the cause of bacteremia and peritonitis in children with chronic nephrosis In one of their patients they were able to grow hemolytic streptococci and pneumococci from the blood on different occasions Moreover chronic nephrosis may be present for years before there is any evidence of infection with pneumococci or it may never be demonstrable Finally another fact which indicates that pneumococcus infections in chronic nephrosis are secondary is that they also occur in the nephrotic type of glomerulonephritis I saw a number of cases of the nephrotic type of glomerulonephritis in which pneumococcus peritonitis developed The origin of pneumococcus bacteremia in patients with chronic nephrosis or the nephrotic type of glomerulonephritis is probably most often the upper respiratory and pulmonary infections from which they frequently suffer The frequency of serious pneumococcus infections in chronic nephrosis has decreased greatly since the introduction of sulfonamides and especially antibiotics

Clausen and Marriott describe cases of chronic nephrosis in children which they believe to be due to infection with Staphylococcus aureus particularly in the paranasal sinuses They have observed excellent results following appropriate treatment of the sinus infection Aldrich[5] also observed prompt improvement in children following the drainage of abscesses resulting from nasal infections Whether all of these cases were actually chronic nephrosis and not nephrotic forms of glomerulonephritis seems open to question And it must be remembered that many cases of chronic nephrosis in children also recover under rational dietary treatment alone Holt and Howland are not convinced of the especial etiological significance of staphylococcus infections of the sinuses I have seen no evidence that infection of the paranasal sinuses is etiologically significant in chronic nephrosis or that treatment of such infection has any effect on the renal disease

Cases presenting the clinical picture of chronic nephrosis are occasionally encountered in tuberculous patients the *nephrite parenchymateuse des tuberculeux* of Landouzy and Bernard[54] It seems probable however that the large majority of these cases are instances of amyloid nephrosis At least this has been my experience though Landouzy and Bernard report such a case with necropsy in which there was no amyloid

Two cases of chronic nephrosis complicating dysentery (type not stated) are included in Rosenberg s series

Trimethadione —Barnett *et al*[55] and White[a] have published instances of the nephrotic syndrome (edema massive proteinuria hypoproteinemia and lipemia) which seemed to result from the therapeutic administration of trimethadione (tridione) and cleared up on withdrawal of the drug The closely related paramethadione (paradione) has also been observed to produce the classical nephrotic syndrome (Wren and Nutt)[22] The production of the nephrotic syndrome by a chemical (noninfectious) agent is of great theoretical interest

Cryptogenic Chronic Nephrosis —In much the largest proportion of the cases the etiology is veiled in darkness The general assumption has been that they are of infectious origin On the other hand Epstein believes that these cases are primarily disorders of metabolism in which thyroid dysfunction plays an important role and that the renal lesions are secondary to the constitutional disease His views are discussed further in the next ection

Thrombosis of the Renal Veins —Of great interest despite its rarity is the production of the nephrotic syndrome in all its details by thrombosis of the renal veins Such cases were first published by Derow *et al*[56] and in the 1939 edition of this book[57] Another example has since been recorded by Shulman *et al*[a] The case I followed occurred in a patient originally observed by Dr Frederick Zeman whom I also had the opportunity of studying On the patient s first admission to the hospital he suffered from migrating phlebitis with thrombosis of the inferior vena cava Subsequently he developed the classical nephrotic syndrome of two years duration with anasarca massive proteinuria hypoproteinemia and lipemia and succumbed to recurrent erysipelas Necropsy disclosed canalized thrombosis of the inferior vena cava and renal veins as well as congestion and lipoidosis of the kidneys Evidently in this case the obstruction to the venous return from the kidneys produced proteinuria sufficient to bring about the nephrotic syndrome I have seen another patient in whom he same diagnosis seemed plausible but there has been no opportunity to verify it

THE NATURE OF CHRONIC NEPHROSIS

Because of the dominant role of proteinuria in the causation of the symptoms of chronic nephrosis discussion of the nature of this malady logically falls into two parts the relation of the proteinuria to the edema and other symptoms and secondly the cause of the proteinuria

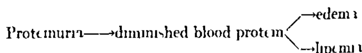
Relation of Proteinuria to the Symptoms of Chronic Nephrosis —By far the most important and often the only symptom of chronic nephrosis is edema The evidence is conclusive that the edema is a consequence of the proteinuria

In the first place the findings reviewed in Chapter 6 have definitely established Epstein's contention that the lower colloid osmotic pressure of the blood plasma due to the diminished albumin content is the essential cause of the edema though other factors undoubtedly also influence the extent of the transudation

Secondly all evidence indicates that the loss of protein in the urine is the primary cause of the diminished protein content of the blood and the change in the relative proportions of the individual blood proteins The protein lost in the urine is almost entirely albumin (over 90 per cent according to Hiller[9] and coworkers) This has been regarded as the explanation of why the albumin fraction of the blood protein is decreased so markedly the conception is that regeneration is rarely able to keep pace with enormous loss through the kidneys Little globulin and no fibrinogen are lost in the urine However Kerr Hurwitz and Whipple[60] have shown that after bleeding fibrinogen is regenerated more rapidly than the other proteins and globulin more rapidly than albumin Also at least some cases of chronic nephrosis are the result of infection and the globulin and fibrinogen content of the blood is increased in many infections These facts perhaps afford some explanation of why the globulins are usually not diminished and may be even increased The question of the rise in fibrinogen is further discussed in connection with the blood chemistry

Thirdly it seems very probable that the lipemia and consequent lipoidosis of the kidneys which are so characteristic a feature of the disease that Munk termed it lipoid nephrosis are likewise consequences of the proteinuria The evidence for this view is discussed on p 473 where it is pointed out that it is still doubtful whether or not the proteinuria produces the lipemia through the intermediacy of hypoproteinemia

At the present state of our knowledge therefore the most probable interrelationship between the fundamental clinical manifestations of chronic nephrosis would seem to be represented by the following schema



It does not seem too much to say that the relationship between proteinuria hypoproteinemia and edema portrayed in this diagram are definitely established questionable is only whether or not the proteinuria produces lipemia through the intermediacy of hypoproteinemia

The Question of Lessened Protein Synthesis in Chronic Nephrosis — Strong evidence summarized above indicates that the primary basis of hypoproteinemia in chronic nephrosis is loss of plasma albumin in the urine However the suggestion has repeatedly been advanced that the protein waste in the urine may be abetted by quantitatively deficient regeneration of plasma albumin (*cf* Bloomfield[61] and Weech *et al* [6]) This conception is based on the observation that hypoproteinemia may persist in nephrotic patients ingesting and assimilating amounts of protein greater than the sum of the protein breakdown in the body plus the protein lost in the urine Actually there seems to be no unequivocal evidence of a *primary* quantitative defect in protein synthesis in chronic nephrosis While there

is no *exact* quantitative relationship between the amount of protein in the urine and the plasma albumin level in the nephrotic syndrome there is a very definite rough inverse correlation In the experience of the writer if the proteinuria of a nephrotic patient falls to 5 grams or less daily and he assimilates an adequate protein diet of high caloric content, the plasma albumin level will rise That this *increase* may be slow and that weeks may pass before it is unequivocal is hardly surprising The plasma proteins are in equilibrium with perhaps several times as much labile protein in the tissues In hypoproteinemic patients both the intravascular and extravascular components of this nondeposit protein pool are depleted In both nephrotic patients (Luetscher[64]) and dogs with nutritional edema (Weech *et al*[65]) a high proportion of infused plasma protein quickly passes from the circulation to the tissues Other factors that may slow and perhaps mask the rise in plasma protein *level* due to regeneration are (1) expansion of plasma volume which is generally lowered in hypoproteinemia and (2) the increase in proteinuria which results from rise in the concentration of plasma protein as long as the kidney do not improve Various clinical observations reveal the great ability of the nephrotic patient to synthesize protein when assimilating a diet containing adequate protein and calories Thus Peters and Van Slyke[48] mention that patients with chronic nephrosis can lose as much as 25 grams of protein daily for several weeks with little change in the level of the plasma proteins I have often seen asymptomatic individuals in whom massive proteinuria had been discovered during insurance or other examinations and had been present for at least months and in whom the plasma proteins were within normal limits Such changes as have been observed in the relative proportions of the plasma proteins in chronic nephrosis (p 471) are probably consequences rather than causes of the proteinuria they are similar in all forms of the nephrotic syndrome whether it results from chronic nephrosis amyloidosis glomerulosclerosis of glomerulonephritis Contrary to an earlier report by Farr and MacFadyen[66] that the plasma amino acid level is low in nephrosis Gottfried *et al*[67] found these protein building blocks normal or even slightly elevated Lyttle *et al*[68] found that 8 of 9 children with chronic nephrosis cleared the plasma of amino acids after injection of casein hydrolysate as quickly as normal controls And Keutmann and Bassett[69] showed that with adequate protein and caloric intake nephrotic patients store large amounts of protein

The available evidence speaks strongly for protein waste in the urine as the fundamental cause of hypoproteinemia in the nephrotic syndrome the role of quantitatively deficient synthesis is still *sub judice* Since experimental plasmapheresis and observations on blood donors (*cf* Co Tui *et al*) indicate that normals with high protein and calorie intake can synthesize as much as 50 grams daily of protein the possibility must be considered that some obscure limiting factor in the synthesis of plasma albumin may exist in the nephrotic patient But it has not been demonstrated

Cause of the Proteinuria of Chronic Nephrosis —The next question that arises is that of the cause of the proteinuria First to be decided is whether the proteinuria is due to an abnormality of the plasma proteins manifesting some extrarenal metabolic disorder or whether the proteinuria is due to

renal disease entailing increased permeability of the kidneys to plasma proteins

The Metabolic Theory of Nephrotic Proteinuria —The theory that chronic nephrosis is primarily a metabolic disturbance dates back to the humoral pathologists of a century ago (see p 127), who believed all varieties of Bright s disease to be primarily blood dyscrasias which produce proteinuria and the renal lesion only secondarily But with the *debacle* of humoral pathology at the hands of Virchow this conception was all but universally abandoned until it was developed in its modern form by Epstein[4] The present-day metabolic theory of chronic nephrosis is entirely due to the brilliant investigations of Epstein who was the first of modern clinicians to appreciate adequately the extent to which copious proteinuria depletes the plasma protein and in turn the great significance of the latter for the pathogenesis of edema in chronic parenchymatous nephritis' More recently a metabolic theory of chronic nephrosis was advanced by the late Thomas Addis [5] who regarded the disease as due to a defect in plasma protein formation and coined the expression prerenal proteinuria

It is known that certain foreign proteins (*e g* egg albumin hemoglobin Bence-Jones protein) free in the plasma are eliminated in the urine (but see p 126) In accord with this fact Epstein believes that chronic nephrosis is primarily a perversion of protein metabolism which so alters the blood proteins that they are eliminated in the urine as foreign proteins To express his belief in the metabolic origin of chronic nephrosis Epstein has termed the disease diabetes albuminuricus He is of the opinion that impairment of thyroid function plays an important role in the genesis of chronic nephrosis In support of this contention he adduces the frequently lowered basal metabolism and beneficial effects he obtained in many cases of chronic nephrosis by the administration of thyroid extract Epstein has found that patients with chronic nephrosis have a remarkable tolerance for thyroid whether given as the extract by mouth or as thyroxin intravenously huge doses may be administered over long periods of time with few or no toxic symptoms and little elevation of basal metabolism Epstein has observed a patient with chronic nephrosis who ultimately develops myxedema and two others in whom chronic nephrosis supervened on prolonged irradiation of the neck involving the chest and thyroid In 8 cases of chronic nephrosis in children Wolbach and Blackfan[6] have found changes in the thyroid consisting in colloid atrophy degeneration of epithelial cells and extreme vascular engorgement But they believe these changes to be merely evidences of functional exhaustion and not specifically related to the nephrosis No structural abnormalities of the thyroid were present in 10 necropsies on nephrotic children collated by Recant and Riggs [7]

Investigations with modern methods do not indicate the presence of hypothyroidism in chronic nephrosis It is true that Peters and Mann[8] found that the protein-bound iodine in the serum is reduced in chronic nephrosis This was also found by Recant and Riggs who further noted that the basal metabolism is low even when calculated on the basis of edema-free weight But they also demonstrated normal or supernormal uptake of radioactive iodine by the thyroid and a rise in the protein

bound iodine level of the serum in response to thyrotropic hormone Recant and Rigg interpret their findings as indicating normal thyroid function in chronic nephrosis—or even hyperactive to compensate for the urinary loss of hormone—and believe that the low protein bound iodine level of the serum is due to hypoproteinemia The amount of hormone lost in the urine is not alone enough to account for the subnormal level of the protein bound iodine in the blood

An observation which would harmonize well with Epstein's view of the primarily extrarenal nature of chronic nephrosis is mentioned briefly by Jungmann In a patient with true chronic nephrosis marked by albuminuria and edema a biopsy on the kidney revealed no anatomical substratum for the symptoms but the necropsy later showed the typical picture of chronic nephrosis Unfortunately this case cannot be adequately evaluated because of the lack of details

The lipemia and the lipoid degeneration in the kidneys has led some authors (e g Loewenthal[5]) to regard chronic nephrosis as primarily a disturbance of lipoid metabolism This theory lacks any substantial basis we have seen that the lipemia most probably is secondary to the changes in the blood proteins

Attractive as is the conception of chronic nephrosis as a general metabolic disturbance it is not supported by direct evidence On the contrary there is strong evidence which speaks strongly against the theory that the proteinuria of nephrosis is not of renal origin

1 Precisely the same changes in the plasma proteins as occur in chronic nephrosis are found in glomerulonephritis and renal amyloidosis two diseases in which the renal origin of the proteinuria would seem beyond cavil

2 In the next section it will be seen that there is ample evidence that the kidney in chronic nephrosis is abnormally permeable to colloids This points strongly to the renal origin of the proteinuria

3 Hayman and Bender[5] found that injection of plasma from three patients with a nephrotic syndrome (one with chronic nephrosis) did not result in proteinuria in healthy recipients

4 The filtrability of molecules through the glomerular membrane is largely determined by their size (p 126) The possibility therefore immediately comes to mind that if the proteinuria of chronic nephrosis is due to abnormalities in the plasma proteins the latter are of molecular size smaller than serum albumin which has a molecular weight of 68 000 and does not pass through normal kidneys However experiments by Addis *et al*[74] designed to test this point failed to reveal the existence of such small protein molecules in either chronic nephrosis or glomerulonephritis

For these reasons the metabolic theory of nephrotic proteinuria seems improbable

Increased Renal Permeability as the Mechanism of Proteinuria in Nephrosis —Proof of abnormal permeability of the kidney is afforded by the passage from the plasma into the urine of significant amounts of substances of large molecular dimension which normally are not so excreted Several such sequences are observed in chronic nephrosis

(a) McClean[77] observed that if gum acacia is injected into the blood stream of a patient with chronic nephrosis it appears in the urine in high concentration which is not the case in health I have repeatedly confirmed this observation

(*b*) Vorzimer, Friedfeld and the writer[78] carried out quantitative observations on the urinary elimination of Congo red a colloidal dye, following intravenous injection In health, the urine contained insignificant traces but in patients with chronic nephrosis and other forms of the nephrotic syndrome the dye appeared in the urine in concentration roughly proportional to the proteinuria

(*c*) Bing[79] showed that if a patient with nephrotic proteinuria is given a blood transfusion the quantity of albumin in the urine is increased while that of globulin is less affected In view of the larger size of the globulin molecules this is what would be anticipated from a rise in permeability of a certain degree In the absence of renal disease blood transfusion is not followed by proteinuria

(*d*) When concentrated human serum albumin is given to patients with cirrhosis of the liver or other conditions not associated with renal disease little or none appears in the urine Similar injections in nephrotic patients are quickly followed by increase in albuminuria Luetscher found that the increased protein excretion following injection of albumin is accompanied by little change in albumin clearance which would indicate that it is eliminated by glomerular filtration

(*e*) In the absence of kidney disease for instance in the xanthomatous diseases increase in the lipid content of the plasma does not result in lipiduria But in chronic nephrosis considerable amounts of lipids pass from the plasma into the urine

The increased permeability of the kidney indicated by the foregoing observations offers a satisfactory explanation of the fundamental phenomena of the nephrotic syndrome It is readily conceivable that the increase in permeability is of such degree as to allow the smaller albumin molecules to pass through much more readily than the larger globulins while the still larger fibrinogen molecules do not filter through at all The lesion would thus produce effects analogous to the experiments of Krogh (p 149) in which he increased the permeability of the capillaries so that they allowed the passage of starch molecules but not of the larger India ink particles The same order of increase in permeability to large molecules occurs in all forms of the nephrotic syndrome—chronic nephrosis diabetic glomerulosclerosis amyloidosis and glomerulonephritis In each proportionately (to the plasma levels) more albumin than globulin enters the urine and fibrinogen does not pass through it all In each lipids and injected colloids enter the urine from the plasma In each the albuminuria produces hypalbuminemia and lowered colloid osmotic pressure of the plasma and the latter results in edema In each lipid and protein (hyaline) droplets appear in the tubular epithelia which is well explained by reabsorption from the filtrate which they have entered as a result of increased permeability Increased permeability of the kidneys to large molecules explains the phenomena of chronic nephrosis so well—and likewise clears up so simply the occurrence of the same nephrotic syndrome in the four conditions of chronic nephrosis renal amyloidosis diabetic glomerulosclerosis and glomerulonephritis—that on mere clinical grounds it may be regarded as established But in addition the urinary excretion of injected serum albumin and other large molecules furnish almost direct evidence of

the increased permeability of the kidney in chronic nephrosis Practically the entire picture of chronic nephrosis seems to be a consequence of leaky kidneys

In the preceding paragraph the expression increased permeability of the kidney is used to designate a state of the kidney in which protein and other large molecules which do not normally pass from the plasma into the urine in more than minute amount (p 119) appear in the urine in much larger quantities The question immediately arises of the mechanism by which in nephrotic proteinuria protein molecules pass in abnormally high concentration into the urine As has been seen on p 131 two mechanisms may be concerned

1 An alteration in the walls of the glomerular loops such that more protein molecules pass through by physical filtration This is perhaps to be regarded as due to the formation in the walls of the glomerular loops of a higher proportion of passages large enough to allow the passage of serum albumin molecules (p 125)

2 Decrease in the capacity of the tubular cells to reabsorb protein from the glomerular filtrate

To the writer it appears that the available evidence points strongly to increased permeability of the glomerular membrane as the fundamental mechanism of nephrotic proteinuria

1 In fixed sections coagulated protein is often found in Bowman's space

2 Of the commonly differentiated plasma proteins albumin shows a far higher clearance than does the much larger globulin molecule and the still larger fibrinogen does not enter the urine at all despite increase in concentration in the plasma Such behavior is in excellent accord with filtration through pores in the glomerular loops It will be interesting to learn how the molecular size of the individual globulins corresponds to their participation in the proteinuria

3 Every function of the tubules that has been studied in early nephrosis when proteinuria is maximal is intact Concentrating ability is excellent Large amounts of ammonia are formed in response to the proper stimulus The urine is highly acid which involves active tubular mechanisms Phenolsulphonephthalein is excreted in high concentration which necessitate tubular excretion There is no defect in the tubular reabsorption of sodium chloride or other electrolytes while the question of glucose reabsorption is still unsettled (p 460) Tm for diodrast and p-amino hippurate are normal Since these variegated tubular functions are without exception unaffected it seems improbable though not impossible that the tubular reabsorption of protein is impaired

4 Bing[50] found that during short periods exogenous creatinin clearance and proteinuria parallel one another Using the less inaccurate endogenous creatinin clearance as a measure of glomerular filtration Elder *et al*[51] made similar observations They found that in the nephrotic patient the albumin clearance is independent of the plasma albumin level Such behavior is much easier to reconcile with filtration as the primary mechanism of proteinuria than with an alteration in tubular transport

5 Eder and his associates calculated the minimum protein content of the glomerular filtrate—on the well warranted assumption that protein is not excreted by the tubules—by dividing the albumin content of the urine by the volume of glomerular filtration (inulin clearance) They found that the glomerular filtrate of nephrotic patients contains between 115 and 505 mg/100 cc which is far above what is believed to be the maximum protein content of the glomerular filtrate in health

The proteinuria of chronic nephrosis would thus appear to be due fundamentally to increased permeability of the walls of the glomerular loops But it is possible that secondarily decreased reabsorption of protein from the filtrate by the tubular cells may augment the proteinuria This could conceivably result from saturation of the protein reabsorbing capacity of tubular epithelia which have taken up enough protein from the filtrate to exhibit "hyalin droplet degeneration" which is not a true degeneration but probably a morphological manifestation of the activity of the cell in taking up protein

The Differentiation of Chronic Nephrosis From Glomerulonephritis — Chronic nephrosis (lipoid nephrosis) was originally recognized as a nosologic entity by Munk Volhard and Fahr and Epstein Very soon after, however Lochlein[8] maintained that lipoid nephrosis is not a separate disease but a variety of glomerulonephritis This opinion has since been supported by Elwyn[53] Bell[54] Moschcowitz[55] and Allen[56] and is widely accepted The thesis that chronic nephrosis does not exist as an independent entity but is one of the forms of glomerulonephritis is largely based on the following supports

1 The widely accepted rarity of cases with the clinical nephrotic syndrome which reveal purely degenerative renal lesions at necropsy (apart from amyloidosis and diabetic glomerulosclerosis)

2 The existence of cases which start as clinically typical acute hemorrhagic glomerulonephritis and then go on to develop the classical picture of the nephrotic syndrome without hematuria hypertension or impairment of renal function Ultimately these patients develop high blood pressure and generally succumb to renal insufficiency necropsy may disclose what is regarded as chronic glomerulonephritis

3 The observation of patients who present the clinical picture regarded as typical of chronic nephrosis—massive proteinuria and edema of insidious onset without hypertension hematuria or impairment of renal function—and nevertheless disclose chronic glomerulonephritis at necropsy

The Anatomical Findings — A chief support of the theory that chronic nephrosis is a variant of glomerulonephritis has been the important investigations of Bell to whom so much of our knowledge of the intimate histology of renal disease is due (p 448) On the basis of histological studies Bell[10] championed the view that chronic nephrosis is actually a variety of glomerulonephritis This investigator and his pupil McGregor performed the valuable service of introducing into the study of the pathological histology of the kidney modifications of Mallory's aniline blue connective tissue stain with this technique the glomerular basement membrane is brought out clearly so that the endothelial and epithelial cells of the glomeruli are more readily differentiated Using this stain

Bell was able to demonstrate in cases of chronic nephrosis in which the glomeruli appeared normal in the hematoxylin-eosin preparation an increase in the number and size of the glomerular endothelial cells and an uneven thickening of the basement membrane As a result of these studies Bell came to the conclusion that lipoid nephrosis is to be regarded as a form of glomerulonephritis in which the glomeruli are damaged but their capillaries are only partially obstructed so that they continue to function and tubular atrophy does not occur Instigated by Bell's findings Kantrowitz and Klemperer[14] studied 2 cases of chronic nephrosis with the staining methods which he recommends However they were unable to demonstrate inflammatory glomerular lesions in either It is true that they found swelling of the glomerular endothelial cells which contained lipoid but these cells *were not* increased in number In the absence of proliferation —which as they point out is not mentioned in 3 of Bell's 4 cases—or cellular *exudation* Kantrowitz and Klemperer do not regard swelling and lipoidal change of the glomerular endothelial cells as evidences of inflammation they found similar changes in Niemann Pick's disease so that these lesions are probably largely manifestations of storage of lipoid derived *from* the lipemic blood Nor do they regard thickening of the capillary loops in itself as indicative of inflammation

Several subsequent investigations have shown that even with the most careful staining technique there are cases *of chronic* nephrosis in which no inflammatory changes in the glomeruli are demonstrable Hitzrot and Read[18] have reported a case of chronic nephrosis in which the staining methods of McGregor and Bell revealed no evidences of glomerulonephritis There was no obstruction of the glomerular capillaries none of the hyaline fibers described by Bell and no cellular proliferation The same was true of cases published in the valuable study of Murphy Warfield and their associates[19] In one of their cases Dr Bell himself found no structural alterations in the glomeruli His opinion was that the appearance of the glomeruli supported our interpretation of lipoid nephrosis In his recent book on Renal Diseases Bell[84] comes to the conclusion that From the histological point of view lipoid nephrosis is different from proliferative glomerulonephritis but it is possible that the histological pictures merely represent different types of reaction to the same irritant *It would thus* appear that the histological evidence does not support the concept that chronic nephrosis is a variety of glomerulonephritis

Regarding the interpretation of the histological findings two further points seem worthy of consideration

1 It is precisely in the classical cases of the nephrotic syndrome under the age of five years that all recent investigators find that lesions of glomerulonephritis are absent In fact in these cases so little change is seen in the glomeruli apart from protein in the capsular space that the microscopic finding *per se* do not suffice to characterize them as abnormal If chronic nephrosis actually started as glomerulonephritis it would be precisely in these cases of relatively short duration in the very young that inflammatory reaction in the glomeruli should be found

2 When patients with a long standing nephrotic syndrome have succumbed and widespread glomerular hyalinization has been found at

necropsy, a diagnosis of chronic glomerulonephritis has often been taken for granted. There can be no doubt that in the past many cases of the Kimmelstiel-Wilson syndrome in diabetics were thus misdiagnosed. Similarly, to the writer it seems that many such cases—in which there is no history of acute glomerulonephritis, in which proteinuria and edema set in insidiously, and in which glomerular hyalinization but no or trivial proliferative changes are found in the glomeruli—are instances of chronic nephrosis, the end stage of the process described in the section on pathological anatomy (p. 448). These constitute at least a very large proportion of the cases included by Ellis in his concept of Type II nephritis (p. 397).

It is widely believed that the diagnosis of chronic nephrosis is made too often and that many, if not all, the cases so diagnosed are actually instances of chronic glomerulonephritis. This belief finds its chief support in the dogma that all glomerular hyalinization apart from that due to arteriolosclerosis is indicative of chronic glomerulonephritis. However, a considerable number of instances of glomerular hyalinization formerly attributed to glomerulonephritis are now known to be due to the totally independent diabetic glomerulosclerosis. Similarly, other instances of glomerular hyalinization represent the end stage of chronic nephrosis. In the opinion of the writer, most of the nondiabetic nephrotic syndromes in the elderly, which are almost always of insidious origin and without a history of acute glomerulonephritis, belong in this group of the hyalinizing end stage of chronic nephrosis.

The Clinical Findings.—Some clinicians have been rendered sceptical of the existence of chronic nephrosis as an independent entity by following cases which for months or years present the classical picture of chronic nephrosis but then develop hypertension and renal insufficiency, succumb to uremia, and reveal at necropsy widespread glomerular hyalinization which is regarded as chronic glomerulonephritis. But limitations in this chain of reasoning should be borne in mind.

(*a*) The clinical picture of the nephrotic syndrome results from depletion of plasma albumin (and the labile tissue protein or protein precursors with which it is in equilibrium) by albuminuria. Such depleting proteinuria may result from chronic glomerulonephritis, diabetic glomerulosclerosis, amyloidosis, or chronic nephrosis. In all these conditions the nephrotic syndrome *per se* is identical; differential diagnosis can only be made by accompanying identifying characteristics of the individual disease. In the cases of chronic nephrosis these are all absent for long periods, i.e., the patients suffers solely from the consequences of the proteinuria, which is why Epstein termed it diabetes albuminuricus. In the large majority of instances of chronic glomerulonephritis one or more such identifying characteristics as history of acute glomerulonephritis, hematuria, hypertension, and impairment of renal function are present in the *early* stages. But there are cases of chronic glomerulonephritis in which for a long period the symptomatology is almost purely that of the nephrotic syndrome resulting from massive proteinuria. In these cases it may be that the glomerular lesion causes relatively little obstruction to blood flow through the glomerular loops while damaging the walls so as to result in increased permeability. The fact that in such cases a differential diagnosis between

glomerulonephritis and nephrosis may be difficult to make for a long time does not gainsay the existence of chronic nephrosis any more than diagnostic difficulties in differentiating rheumatic from other forms of endocarditis speaks against the independent existence of the endocarditis of Libman-Sacks disease or subacute bacterial endocarditis

(b) The fact that a patient with the nephrotic syndrome develops hypertension or impairment of renal function going on to uremia has almost universally been taken as *prima facie* evidence that glomerulonephritis is present Such an inference is unwarranted Any diffuse glomerular disease may produce hypertension or renal insufficiency *e g* diabetic glomerulosclerosis and amyloidosis Similarly the hyaline thickening of the capillary basement membrane in chronic nephrosis (p 448) may ultimately so impede glomerular blood flow and obliterate so much of the filtering area that hypertension and renal insufficiency result For beautiful examples of such a sequence of events the reader is referred to the study of Bahr[5] carried out in the clinic where the histology of the glomerulus has been studied most carefully

It also appears significant that the classical nephrotic syndrome may have a noninfectious etiology (tridione p 455) which is not true of glomerulonephritis

The evidence at hand thus indicates strongly that the glomerular lesions of chronic nephrosis are not manifestations of chronic glomerulonephritis They are noninflammatory alterations in the basement membranes of the loops going on to hyalinization and their etiology is in most instances obscure

Summary – The foregoing discussion of the pathogenesis of chronic nephrosis may be summarized briefly as follows

The edema of chronic nephrosis is a consequence of the proteinuria

The proteinuria is due to abnormally great permeability of the walls of the glomerular loops to large molecules permitting the filtration of plasma proteins into the urine If decreased tubular reabsorption of protein from the glomerular filtrate plays any part in the pathogenesis of the proteinuria it is secondary

The cause of the preternatural permeability of the walls of the glomerular loops to large molecules is a noninflammatory alteration which is not definitely recognizable microscopically at a stage when it has already produced massive proteinuria but then goes on to hyaline thickening of the basement membrane

In cases of true chronic nephrosis there is neither anatomical nor symptomatic nor anamnestic evidence that the damage to the glomerular loops is the outcome of antecedent glomerulonephritis

The histological prominence of the lipidosis and hyaline droplet formation in the tubular cells has led to exaggerated estimation of the severity of the degenerative changes in the epithelium of the tubules The lipidosis and hyaline droplet formation are probably largely a manifestation of reabsorption of lipid and protein from the glomerular filtrate *i e* of functional activity None of the known functions of the tubules is impaired in chronic nephrosis

The functional characteristics of the renal alteration in chronic nephrosis are

1 Increased permeability to colloids of the glomerular loops evinced by proteinuria and lipiduria

2 Unimpaired renal blood flow until late stages of the disease when hyaline thickening of the basement membranes obliterates glomerular loops

3 Unimpaired tubular function likewise until the late stages when the renal circulation is impeded

Inasmuch as the lesion of glomerulonephritis can produce this combination for a long time it is not surprising that this disease often simulates chronic nephrosis for years

THE CLINICAL PICTURE OF CHRONIC NEPHROSIS

As a rule the clinical picture of chronic nephrosis in the early stages is peculiarly monotonous albuminuria and edema are the outstanding manifestations waxing and waning with or without obvious reason over periods of months or years until the sufferer finally recovers or goes on to renal insufficiency and uremia The patient is weak and often pallid though examination of the blood does not usually reveal as severe impoverishment in hemoglobin as the pallor would suggest It is in chronic nephrosis that the nephritic facies —the combination of waxy pallor with edema—is seen in perhaps its most classical form

Onset — The onset is usually insidious The patient feels weak and tires readily over a period of time which may be weeks or months but usually does not go to the doctor until he notices an edematous swelling In young children the disease is most often discovered when the mother notes the dropsy the child often feels well and is playful In adults the proteinuria is not rarely found in an insurance or other examination when there is no edema or subjective symptom Rarely in children the disease has a sudden clinical onset with peritonitis or another infection In the syphilitic cases the first evidence of the disease may be the finding of protein in the urine in a routine examination during the course of antisyphilitic treatment Or edema may be noted at the same time as the rash sore throat or other manifestations of the secondary period of syphilis appear

Edema —Edema is the central feature of chronic nephrosis to the patient it is the disease The hydropic swelling may start in the feet or in the face and usually spreads so as to become very extensive It is peculiarly soft edema and the impression made by the finger is slow to disappear The scrotum or vulva may become enormously swollen Usually the serous sacs notably the peritoneum are also involved The edema may almost completely disappear from the skin while the ascites persists It is possible that some of the gastro intestinal disturbances of which the patients often complain are due to edema of the mucous membrane but I have not seen this proved I have once seen edema of the retina

The extent of the edema varies greatly Often diminution is attributable to therapeutic measures but in other instances there is no obvious explanation for the onset of diuresis and lessening of the edema Then the

edema may increase again though the regimen has been changed in no way The edema may decrease following an acute infection (p 492)

The edema fluid obtained from under the skin by puncture is usually clear but may be opalescent That in the peritoneum and less often in the pleura is almost always opalescent appearing like slightly soapy water In other instances the ascites is decidedly milky Gallavardin Delore and Josserand[87] observed a milky peritoneal transudate with clear subcutaneous edema and cerebrospinal fluid an association which I have also encountered The opalescence is not removed by shaking with ether It is probable that this opalescence is due to the presence of a globulin lipoid compound (Wallis and Schoelberg[88]) although Bruger[89] found no evidence of cholesterol protein complexes in such fluids The specific gravity of the fluid is very low

The extremely low protein content of the fluid is characteristic (Epstein Beckmann[90]) There is usually less than 0 1 per cent of protein and several times I have found the protein content too low to be determined quantitatively Krogh[91] refers to a case of chronic nephrosis in which the edema fluid was protein free As Schmidt[8] pointed out three-quarters of a century ago the fluid of the ascites and hydrothorax contains much more protein than the anasarca fluid of the same patient Thus Epstein found that the effusions into the serous sacs in chronic nephrosis averaged 0 255 per cent protein all of which was globulin While this protein content was higher than that of the anasarca fluid it was much lower than that present in serous effusions due to cardiac failure in which Epstein found the protein content to average 3 3 per cent

It has been seen (p 456) that nephrotic edema is correlated with the diminished colloid osmotic pressure of the blood plasma resulting from the drop in the plasma albumin The correlation is not always obvious from the total protein content of the blood because the factor of change in the proportions of the individual protein fractions is of primary importance 1 gram per cent of globulins exerts far less colloid osmotic pressure than does 1 gram per cent of the smaller albumin molecules However edema is apparently always present when the plasma protein content in nephrosis is less than 4 per cent (Linder[92] *et al*) and almost always when the plasma proteins fall below 5 per cent (Epstein) On the other hand there may be nephrotic edema with almost 6 per cent of protein in the plasma if as happens in unusual instances this is mostly globulin The closest correlation is with the plasma albumin level when the latter is below 2 5 per cent edema is rarely absent in a nephrotic patient In children Gottfried *et al*[93] found that a rise in total protein above 4 0 or albumin above 1 5 per cent is almost invariably associated with decrease in edema while a fall below these concentrations is almost always accompanied by increase in edema Of course at any plasma albumin level the extent of the edema is influenced by other factors notably sodium intake and therapeutic measures which result in great changes in edema despite little alteration in plasma albumin concentration The question is discussed in more detail on p 457

Urine —The urine is greatly diminished in volume while edema is forming or during periods when it is being held in check by fluid restriction For

weeks at a time the daily urinary output may be around 300 or 400 cc. Corresponding to fluctuations in the edema the urinary volume varies. As the edema diminishes there may be marked polyuria. The urine is generally more or less cloudy and often of a smudgy brown color. On standing, it usually decomposes rapidly with the development of a nauseating odor.

During the oliguric periods the specific gravity of the urine is high even after allowance is made for the protein present. Values over 1.030 are not very uncommon. The color is correspondingly deep and a copious sediment of urates is often deposited. The urine is highly acid. As long as edema is forming the concentrations in the urine of sodium, chloride and bicarbonate are low while those of urea, potassium, phosphate and hydrogen ions are high (*cf.* Fox and McCune[94]). With discharge of edema these changes are reversed. The alterations in the urinary solutes during accumulation of edema are compatible with simultaneous expansion of extracellular fluid volume, cellular dehydration and augmented protein breakdown.

Proteinuria.—Proteinuria is a cardinal feature of chronic nephrosis. As a rule, the quantity of protein lost in the urine is very great. In fact the highest degrees of proteinuria are observed in this disease, particularly in the syphilitic cases. One of Epstein's patients lost from 18.2 to 26.[illegible] grams of protein in the urine daily for several months. In Descoust's[95] case of syphilitic nephrosis there was the enormous amount of 110 grams of protein in 800 cc. of urine. Values of 2 per cent or more are not uncommon. The urinary protein is largely albumin. Hiller, McIntosh and Van Slyke[59] found that albumin constitutes over 90 per cent of the total urinary protein, a higher proportion than they found in other varieties of renal disease. The great predominance of the small albumin complexes in the urine in chronic nephrosis is also shown by measurements of the colloid osmotic pressure. Electrophoretic studies by Longsworth,[96] Luetscher,[97] Malmros and Blix[98] and Routh[99] show the same peaks in the urine for albumin and alpha, beta and gamma globulins as does the plasma; fibrinogen, however, is absent despite elevated concentration in the plasma. The Tiselius pattern reveals an even higher proportion of the urinary protein to be albumin than does the Howe fractionation. Only when the plasma albumin falls to extremely low levels is the preponderance of albumin in the urinary protein not so great. Estimations of the molecular weight of the urinary albumin by Longsworth and MacInnes[100] indicate that it is less than of the albumin in the plasma; perhaps the smaller molecules are the more readily filtered. During the administration of plasma or concentrated serum albumin the urinary albumin content rises. Blackman and Davis[101] found the gamma globulin fraction very low in a patient with chronic nephritis while it was much higher in rapidly progressive cases of the nephrotic form of glomerulonephritis; they suggest that the precipitation of gamma globulin, which is the fraction most readily thrown down by the usual protein precipitants, may be concerned in rapid progression of a nephrotic renal disorder.

The proteinuria varies greatly from time to time. Diminution in proteinuria is usually accompanied by improvement of the patient, but it is prone to increase again. The relation of the proteinuria to the diet is discussed on p. 122.

Slight and transient *glycosuria* is not uncommon Hiller[102] showed that the urinary sugar in these cases is actually glucose. As Hetenyi[103] found and I have several times confirmed patients with chronic nephrosis almost always exhibit alimentary glycosuria after the ingestion of 100 grams of glucose and often after 50 grams. Strauss[104] also found the renal threshold for sugar abnormally low in chronic nephrosis; his studies were carried out by the oral administration of glucose. Hawkins, MacKay and Van Slyke[105] demonstrated an abnormally high content of fermentable sugar in the urine of patients with chronic nephrosis; in 3 of their 6 cases there was gross glycosuria, the urine in the fasting state containing over 0.3 per cent of fermentable sugar and more than 1 per cent following the ingestion of 1 gram of glucose per kilogram body weight. The glycosuria is a renal glycosuria, for in several such instances in which the blood sugar was determined the concentration in the blood did not reach the normal renal threshold for this substance. Possibly the tubular lesions interfere with the resorption of sugar from the glomerular filtrate. It should be mentioned, however, that the renal nature of the alimentary glycosuria in chronic nephrosis is contested by Fell,[106] who found the renal threshold for glucose elevated and not lowered in this disease. His studies were carried out by the intravenous injection of glucose solution. It is not clear why this method should show a different renal threshold than that observed after the ingestion of glucose, so the question demands further study.

Urinary Sediment.—Of notable interest is the presence in the sediment of *doubly refractile lipoids* first described by Munk. The examination of the sediment for doubly refractile bodies is very simple, requiring only the use of the polarizing device which can be attached to any microscope. Viewed through the usual light, doubly refractile lipoids cannot be distinguished from fat and may pass for the ordinary granulations of a granular cast, but through polarized light (i. e., light that has passed through crossed Nicol prisms) they appear light in an otherwise dark field. Many of the light areas of doubly refractile lipoid are divided into four light segments by a dark Maltese cross. The anisotropic lipoids occur as free droplets or larger aggregates, or in casts, which appear in ordinary light as granular or fatty casts. Crystals may also light up through the crossed Nicol, but their nature is usually readily ascertained through ordinary light or, as Munk suggests, they may be removed by washing the sediment with physiological salt solution. As further *sources of error which are* readily avoided Munk mentions hairs, bits of wool and soap bubbles.

Notable quantities of doubly refractile lipoids occur in the urine not only in chronic nephrosis but also in other conditions in which there is lipoid degeneration of the renal epithelium, i. e., diabetic glomerulosclerosis, the nephrotic type of glomerulonephritis and, less commonly, in amyloid nephrosis. Isolated anisotropic droplets found on one occasion are of little significance, occurring in many conditions; only the presence of considerable quantities in a single examination or of small amounts on repeated occasions is diagnostic of widespread lipoid deposition in the tubules.

The amount of anisotropic lipoids present in the urine in chronic nephrosis varies greatly; at times there may be little or none, while soon after

weeks at a time the daily urinary output may be around 300 or 400 cc. Corresponding to fluctuations in the edema, the urinary volume varies. As the edema diminishes there may be marked polyuria. The urine is generally more or less cloudy and often of a smudgy brown color. On standing, it usually decomposes rapidly with the development of a nauseating odor.

During the oliguric periods the specific gravity of the urine is high, even after allowance is made for the protein present. Values over 1.030 are not very uncommon. The color is correspondingly deep and a copious sediment of urates is often deposited. The urine is highly acid. As long as edema is forming the concentrations in the urine of sodium chloride and bicarbonate are low, while those of urea, potassium, phosphate and hydrogen ions are high (*cf.* Fox and McCune[94]). With discharge of edema these changes are reversed. The alterations in the urinary solutes during accumulation of edema are compatible with simultaneous expansion of extracellular fluid volume, cellular dehydration and augmented protein breakdown.

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amyloid nephrosis The loss of blood proteins in these conditions combined with the efforts of the body to regenerate the proteins and perhaps to compensate in other ways for their loss produces characteristic changes in the proteins and lipids of the *plasma* The resulting nephrotic blood picture as it may be termed consists essentially in the following

1 *Decrease* in the total protein content of the plasma usually entirely at the expense of the albumin fraction with resultant inversion of the albumin to globulin ratio

2 Alterations in the proportions of the globulins

3 Increase in the fibrinogen content of the plasma

4 Decrease in the colloid osmotic pressure of the plasma

5 Increase in the velocity of sedimentation of the red blood cells

6 Increase in the concentration of fats and lipoids in the plasma

It is interesting to note how well the older clinicians were acquainted with these abnormalities of the blood resulting from copious proteinuria the discovery of which we are inclined to attribute wholly to modern chemical research Thus Bostock[114] points out in Bright s first memoir that the blood is deficient in protein Bright s contemporaries were aware of the increase in fibrinogen in the blood of patients with marked proteinuria in what seems to have been a case of chronic nephrosis Schmidt[9] found 1 03 per cent of fibrin Christison[115] demonstrated the lipemia of such individuals

1 The decrease in the total protein content of the plasma is usually striking Instead of the normal 7 per cent or more of protein there may be well under 3 per cent in severe cases It has already been mentioned that the drop in total protein is mostly or more often entirely due to diminution in the albumin fraction (see p 456) The albumin concentration of the plasma may fall below 1 per cent in extreme instances The result is that the albumin content of the plasma is diminished more than the globulin almost always the albumin/globulin ratio the normal value of which is from 1 5 to 2 5 is inverted (Epstein) and may even sink below 0 2 In fact for a time the total protein content of the plasma may not be lowered although there is already inversion of the albumin to globulin ratio the drop in albumin is masked by an increase in globulin and fibrinogen In a remarkable instance of chronic nephrosis studied by Salvesen [116] regeneration of globulin more than compensated for loss of protein in the urine so that hyperproteinemia (8 97 to 10 73 per cent of plasma protein) resulted with an albumin to globulin ratio of only 0 23 to 0 26

Actually the albumin/globulin ratio is at least often decreased even more than is indicated by the usual salting out procedure Luetscher[97] found electrophoretically that when albumin is decreased and alpha globulins increased the latter may contaminate what is regarded as the albumin fraction by salting out and lead to overestimation of the albumin content Some of the supposed discrepancies between the tendency to edema formation and the plasma albumin level may be due to such misinterpretations resulting from Howe estimations

2 The total globulins are more *often increased* than decreased Electrophoretic studies have revealed marked alterations in the proportions of the individual globulins (Longsworth [98] Luetscher [97] and Blix[117]) Usually the

they are readily demonstrated. Gainsborough[107] found that while the urine normally contains from 1.7 to 4 mg. of cholesterol per day, the elimination in renal disease may be up to 41 mg. daily. Bruger[109] showed that the urinary lipids include cholesterol, fatty acids and phospholipids and that all three lipids tend to vary in parallel fashion. Lipiduria occurs only in the phases of renal disease with pronounced proteinuria (apart, of course, from chyluria). Lipidemia in the presence of healthy kidneys does not produce lipiduria. Thus in a diabetic with lipidemia so severe as to produce lipemia retinalis I was unable to find lipids in the urine. Lipiduria in the nephrotic syndrome has a twofold origin: desquamation of tubular epithelium in which lipids have been deposited and filtration of plasma lipids. The derivation of some of the urinary lipids from desquamated cells is sometimes revealed by the finding in the sediment of renal epithelia containing lipid droplets. As a rule, however, the plasma is doubtless quantitatively a much more important source of the urinary lipids. This was indicated by the finding of Gross[108] that if a patient with chronic nephrosis or the nephrotic type of glomerulonephritis ingests 5 grams of cholesterol the quantity of lipids in the urine increases greatly within a few hours. In diseases not characterized by massive proteinuria Gross did not find lipiduria after ingestion of lipid. There is every reason to believe that in the nephrotic syndrome lipiduria, like proteinuria, is a consequence of the increased permeability of the glomeruli. This conception of the filtration of lipids from the plasma into the urine is strongly supported by the finding of Bruger[109] and Bing and Starup[110] that the excretion of lipids parallels that of protein, as well as the observation of the latter investigators that the cholesterol excretion parallels the urea and creatinin clearances.

The number of casts present differs: at times there are numerous hyaline, granular and fatty casts, while on other occasions they are almost entirely absent. Leukocytes are usually present. Of great importance in the differential diagnosis from glomerulonephritis is the fact that red blood cells are completely absent or present in but very small numbers; well marked hematuria does not occur in chronic nephrosis apart from rare transitory episodes in which intercurrent infections may be concerned. But that small numbers of erythrocytes do not rule out lipoid nephrosis is shown by Farr's[111] Addis counts which disclosed an increased number of red cells in 19 of 36 children in whom he had made a diagnosis of nephrosis after six years observation. Carrying out Addis counts, Landis and Elsom[112] found that 3 patients with the nephrotic syndrome excreted between 200 000 and 800 000 red blood cells in twelve hours, which was much less than comparable patients with glomerulonephritis.

The Blood.—In chronic nephrosis there are abnormalities in the chemical composition of the blood which are of fundamental theoretical and practical importance. These changes involve primarily the proteins and lipids of the plasma (*cf.* Gutman[113] for a scholarly study of the plasma proteins in disease). The abnormalities in the plasma proteins and lipids evidently results from the loss of protein in the urine and are identical with those found in other diseases with copious and protracted proteinuria; namely, diabetic glomerulosclerosis, the nephrotic type of glomerulonephritis and

features of chronic nephrosis and the nephrotic type of glomerulonephritis An exception is found in emaciated patients in whom they may be absent for reasons which will be discussed in the next paragraph In amyloid nephrosis in which there is usually severe emaciation the cholesterol content of the blood is most often not elevated but if the patient is well nourished it may be high (p 523) In patients with amyloidosis or glomerulonephritis the development of renal insufficiency is usually accompanied by fall in the cholesterol content of the blood In chronic nephrosis the concentration of cholesterol in the blood is often over 500 mg per cent and in rare instances may even exceed 1000 mg per cent (normal less than 200 mg per cent) In fact in a patient studied by Dr George Baehr and seen by the writer the cholesterol content of the blood attained the immense height of 2300 mg per cent * According to the studies of Gainsborough[107] and Lichtenstein and Epstein[1..] there is no characteristic change in the ratio of esterified to total cholesterol which may fluctuate within wide limits In some of the patients studied by the latter investigators as high as 80 to 90 per cent of the cholesterol was in ester form During recovery the hypercholesteremia may long outlast the hypalbuminemia The content of the blood in fatty acids is even more increased than in cholesterol The phosphatides are likewise elevated Thus in a case of chronic nephrosis Knauer[35] found in the blood a total of 4700 mg per cent of fatty substances of which 2500 mg per cent was fatty acids while cholesterol and phosphatides each constituted about 1000 mg per cent In studies with accurate methods Page Kirk and Van Slyke[1 6] found that in the nephrotic syndrome free cholesterol cholesterol esters phosphatides and neutral fats rise and fall together Not only is the cholesterol content of the blood increased in chronic nephrosis but it is also found in abnormally great quantities in the adrenals (Guy Laroche[1 7]) and may be deposited in atheromatous patches in the arteries of young persons (Loewenthal) We have already mentioned that lipoid may also be present in edema fluid in these cases

The pathogenesis of the lipidemia of the nephrotic syndrome requires further investigation Hiller[128] and her coworkers showed that the lipemia of chronic nephrosis is not the result of inability of the body to burn fat The low basal metabolism found by Epstein and Lande[129] in some nephrotic patients is not closely correlated with hyperlipemia Heymann and Clarke[13] observed lipemia following nephrectomy or renal damage by poison but it is difficult to see the connection of this with the nephrotic syndrome in which lipemia is present while renal function is unaffected and tends to disappear if azotemia develops F H Fishberg[131] and the writer found that in experimental lipemia produced by bleeding rabbits the rise

* Cholesterol is a comparatively insoluble substance but nephrotic plasma carries it in solution in larger quantities than normal plasma can dissolve (Hanger[12]) The state in which such large concentrations of cholesterol are held in solution remains to be elucidated Perhaps relevant is the recent finding of Rosenman et al[1..] that whenever hypercholesteremia exists in the nephrotic syndrome (lipoid nephrosis glomerulonephritis diabetic glomerulosclerosis) as well as in other hypercholesteremic states the cholic acid content of the serum is increased They found the bile acid content of the serum similarly increased in experimental nephrosis produced in rats by rabbit anti rat kidney serum

alpha and beta globulins are markedly increased and the gamma globulins decreased while variable changes are reported in alpha₁ globulins. To some extent these changes in the globulins may be secondary to the albumin depletion for Routh *et al* [99] observed that they may be temporarily reversed by injection of concentrated serum albumin. The high beta globulin peak is partly correlated with the lipemia for Longsworth and others have found that it is lowered after ether extraction. With the ultracentrifuge Lewis and Page [6] found that in the nephrotic syndrome there is great increase in concentration of the S 70 40–70 and beta and alpha lipoproteins. The frequently very low gamma globulin content may play a part in the susceptibility of nephrotic patients to infections for many antibodies are included in the gamma globulin fraction.

3 Kollert and Starlinger[118] pointed out and others have confirmed that in chronic nephrosis there is an increased fibrinogen content of the plasma. Normally the plasma contains less than 0.3 per cent of fibrinogen while in chronic nephrosis Kollert and Starlinger found as much as 1.19 per cent. The cause of the rise in fibrinogen is not definitely known. Fibrinogen is increased in the blood in many infections but it scarcely seems that this factor can account for the great increase seen in chronic nephrosis. Kollert and Starlinger believe the increase in fibrinogen to result from increased destruction of tissue protein which according to these authors occurs in chronic nephrosis. The explanation seems hypothetical (see also p 456)

4 That the colloid osmotic pressure of the blood plasma is markedly decreased in chronic nephrosis was pointed out by Epstein on the basis of his observations of the decreased protein content of the plasma. This decrease in colloid osmotic pressure and its relation to the edema have been repeatedly established by direct measurements which have revealed that the fall in colloid osmotic pressure is proportionately greater than the drop in protein content. These researches are summarized on p 157

5 Kollert [119] Salomon[120] and others have shown that the sedimentation time of the red blood cells is markedly diminished in the nephrotic syndrome. Some of the fastest sedimentation rates are seen in this condition a Westergren sedimentation rate of over 120 mm per hour is not rare. This is evidently a result of the changes in the colloids of the plasma in fact Salomon has shown that a relative rise in the globulin fraction is practically always accompanied by decreased sedimentation time. The high fibrinogen and low albumin contents of the plasma may also be concerned for these changes in the plasma proteins have been observed to be related to acceleration in the sedimentation rate. Block *et al* [9] found that in nephrotic children acceleration of the sedimentation rate is more closely correlated with fall in albumin than with rise in fibrinogen.

6 The milky appearance of the blood serum in some nephropathies with copious proteinuria was observed first by Blackall[39] and Bostock[114]. Christison[115] showed that it is due to the presence of fat in the serum. This may be but slightly cloudy or almost milky. That this lactescence of the serum is due not only to fat but also to lipoid was shown by Port and Chauffard *et al* [111] who found that there may be marked hypercholesteremia. The lactescent appearance of the serum is probably due to the formation of a lipoid globulin compound. Lipemia and lipoidemia are almost constant

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they are altered Blackfan and Hamilton[135] and Atchley and Benedict[136] long ago found depression of *total base* in some cases This diminution in total base is due to retention in sodium Fox and McCune[84] found the average serum sodium of their nephrotic children 132 mEq per liter as contrasted with their normal average of 142 mEq There is little change in the *potassium* content of the serum (Kohn[137]) Salvesen and Linder[138] showed that the serum calcium content is depressed less than 9 mg per cent is not rare and values as low as 3 5 mg per cent occur Salvesen and Linder correlated the hypocalcemia with hypalbuminemia the fraction of the calcium which is bound to protein is lowered This interpretation is supported by the finding of Gottfried *et al*[87] that the serum calcium phosphorus and protein values in nephrotic children accord with what would be anticipated from Peters and Eiserson s empirical equation for the relation between these variables That the ionized calcium of the blood is not decreased in *chronic nephrosis* is also indicated by the great rarity of tetany and was proved by McClean and Hasting[140] by experiments on the frog s heart *Phosphate* and *sulfate* are usually but little changed Among the anions Atchley and Benedict observed long ago that *chloride* may be elevated and *bicarbonate* depressed and similar findings have recently been obtained by Fox and McCune Atchley and Benedict observed that administration of chloride leads to very pronounced rise in the plasma level of this ion On the other hand Peters[139] found the alterations in chloride and bicarbonate very variable with their sum usually unchanged and in nephrotic children Gottfried *et al* found them almost always within normal limits

In recent years since the flame photometer has made sodium and potassium determinations more or less routine the writer has most often seen little changes in the electrolyte apart from hypocalcemia in the uncomplicated nephrotic syndrome resulting from lipoid nephrosis especially in children Usually only when hypoproteinemia is complicated by renal insufficiency due to glomerular hyalinization or some such transitory prerenal factor as vomiting diarrhea or infection do significant fall in bicarbonate and sodium and rise in chloride appear Peters long ago pointed out that with clinical improvement the plasma base and bicarbonate tend to return to normal even though albuminuria and hypalbuminemia persist While the lowered albumin content of the plasma affects the electrolyte concentrations through the mechanism expressed in Donnan s formulation the changes due to this factor alone apparently are not marked

Gottfried *et al*[87] found the serum *carotene* level elevated in most nephrotic children this may be correlated with the lipemia

As regards the *blood volume* older observations of Brown and Rowntree[1] with the dye method indicated that in the absence of anemia the blood and plasma volumes are normal but when there is anemia both these volumes are increased However in the nephrotic syndrome the dye method is probably even less reliable than under other circumstances because of the rapid departure of colloidal dyes from the circulation (cf next paragraph) Using the carbon dioxide method Waterfield[141] found the blood and plasma volumes lowered in the nephrotic stage of chronic glomerulonephritis in which the conditions are presumably anal

in fat and lipoid is correlated with fall in plasma protein. In these experiments it was found that the fat and lipoid accumulating in the blood were derived not only from the food but also by mobilization from the subcutaneous tissue and other fatty depots, which were completely stripped of their normal fat. In chronic nephrosis in humans there is also loss of the subcutaneous fat, though it is masked by the edema, and it seems probable that the mechanism of nephrotic lipemia also consists in mobilization of lipids into the blood from the food and the lipid depots consequent on the fall in blood protein. It may be that the lowered protein content of the plasma creates physical conditions which favor the migration of lipids into the plasma. A teleological explanation of the lipid mobilization is yet unproved, as that it is an effort on the part of the body to increase the abnormally low colloid osmotic pressure of the plasma that results from the loss of protein in the urine. According to this theory the reason for the frequent absence of lipemia in emaciated patients with low blood protein—notably those with amyloid nephrosis—is the paucity of fat in the depots and the poor appetite of most such individuals, so that little lipid is available for mobilization into the blood stream. Evidence indicating that the lipids of the plasma actually exert a colloid osmotic pressure has been advanced by A. H. Fishberg,[13] although Peters[133] believes that this pressure is small. Keys and Butt[134] find that the capillaries of man are as impermeable to the serum lipids as they are to proteins, but nevertheless were unable to demonstrate that the lipids exert a colloid osmotic pressure.

However, this conception, that the lipemia of the nephrotic syndrome is a consequence of the hypoproteinemia, has not been generally accepted. Strongly opposed to it is the finding of Leiter that when the plasma proteins of the dog are depleted by plasmapheresis the blood cholesterol does not rise. Moreover, Page, Kirk and Van Slyke,[116] Bing and Starup,[110] and Peters and Mann[3] found no close correlation between plasma protein deficit and lipemia in the nephrotic syndrome. Hypoproteinemia due to undernutrition in man is rarely accompanied by lipemia. While these facts speak against the theory that nephrotic lipemia is a consequence of hypoproteinemia, they do not rule it out, because the development of lipemia may be prevented by undernutrition and consequent exhaustion of the fat depots. Clinical observations indicate that the lipemia is in some way a consequence of the proteinuria. I have repeatedly observed that diminution in proteinuria for more than a transitory period is accompanied by decrease in lipemia. When a patient with the nephrotic form of glomerulonephritis develops renal insufficiency, the resulting decrease in proteinuria is associated with diminution in lipemia.

The *crystalloids* of the blood are usually less affected unless the patient goes on to the stage of glomerular hyalinization with renal insufficiency. Until this late stage the *urea* and *nonprotein nitrogen* levels are within normal limits. During pneumococcus peritonitis or other complicating infections or as a result of vomiting or diarrhea from any cause, transitory azotemia may develop. The administration of urea as a diuretic in combination with high protein diet often raises the blood urea.

The *electrolyte* constellation varies considerably from case to case. Often the electrolytes are within normal limits, while in other patients

urea clearances were not observed in patients over eighteen years of age. Since Emerson *et al* found that the high urea clearance accompanied correspondingly increased renal blood flow (diodrast clearance) and glomerular filtration (inulin clearance) they concluded that the increased urea clearance in nephrotic children is due to augmented renal blood flow. That the increased filtration is not purely a consequence of decreased colloid osmotic pressure of the hypalbuminemic plasma is shown by Emerson's observation that it may persist long after the plasma proteins return to normal. And O'Leary and Corcoran[146] have found that renal blood flow and glomerular filtration change little when the plasma proteins of dogs are diminished by plasmapheresis.

Such tubular functions as have been studied in lipoid nephrosis are likewise intact (except perhaps for occasional defect in glucose reabsorption p 469). Good tubular function is immediately indicated by the high specific gravity and acidity of the urine and its low chloride content in the absence of hypochloremia. Magnus-Levy[147] showed that the ability of the tubules to synthesize ammonia is not impaired. By comparative inulin and creatinin clearances Emerson *et al* demonstrated that tubular excretion of creatinin is increased in nephrotic children.

As mentioned above transitory impairment of renal function with azotemia may result from vomiting diarrhea or infection. Only in those cases which go on to extensive hyalinization of the glomeruli do permanent impairment of renal function and uremia develop.

Basal Metabolism —Oxygen consumption is often lowered in chronic nephrosis (Epstein) even after allowance is made for the edema (Peters and Van Slyke[148]). Most often the lowering is but slight values such as −20 per cent being found though even lower oxygen consumption may be present. In other cases the basal metabolism is normal. Epstein's views on the nature of the metabolic disturbance in chronic nephrosis are discussed on p 458. Another factor that may also be concerned in depressing the basal metabolism in chronic nephrosis is undernutrition. Most patients with chronic nephrosis suffer from undernutrition and protein starvation (Peters[149]). One of the mechanisms by which the organism adapts itself to undernutrition is by depressing oxygen consumption. Other factors that may be concerned in decreasing oxygen consumption are heat insulation by extensive subcutaneous edema (Moschcowitz[7 2 9]) and the barrier offered by the edema fluid to the diffusion of oxygen from blood to tissues as brought out by Harrison and Pilcher (p 146).

General Condition —For a long time the patient may feel relatively well the edema being the only complaint. One is often surprised how edematous children play without discomfort. But after a variable time weakness appears and may become extreme. The emaciation is actually very great but is usually hidden by the edema. The appetite is as a rule very poor which renders the all important abundant feeding of the patient very difficult. This difficulty is sometimes enhanced by vomiting and diarrhea perhaps due to edema of the gastro intestinal mucous membrane. After a time most adults become discouraged and despondent because of the apparently interminable dropsy for which the physicians seem able to do so little.

ogous to those in chronic nephrosis Observations of low plasma volume in the nephrotic syndrome have also been made by Luetscher[18] and by McClure[19] *et al* this seems to be at least the rule while edema is forming or being maintained

Colloidal dyestuffs injected into the blood stream of patients with chronic nephrosis disappear from the circulating blood with great rapidity The rapid disappearance of Congo red from the blood stream was introduced as a test for amyloid disease by Bennhold (see Chapter 18) but it also occurs in chronic nephrosis and the nephrotic type of glomerulonephritis Thus one hour after the intravenous injection of Congo red into a patient with chronic nephrosis, only 18 per cent of the dye remained in the blood stream instead of a normal of 70 per cent or more The cause of the rapid disappearance is discussed in Chapter 18 and p 460

Clausen[142] and Leiter[143] have found that the *surface tension* of the blood serum is lowered in chronic nephrosis, a phenomenon which probably results from the diminished protein content

Anemia —Despite the striking pallor of most patients with chronic nephrosis anemia in contrast to glomerulonephritis is present in only part of the cases and is most often not marked Brown and Rowntree[111] found the hemoglobin content of the blood normal in 5 of 9 cases of chronic nephrosis while the anemia was but mild in the others In a subsequent study using more rigid criteria for the diagnosis of chronic nephrosis Wilbur and Brown[144] observed anemia in but 1 of 25 cases a proportion which is well below my experience In some cases particularly if there has been long-continued dietary restriction the anemia may be very severe Contrary to azotemic anemia it is a hypochromic anemia with a low color index

Blood Pressure —The blood pressure is normal in chronic nephrosis in children and usually for years in adults But in those cases which go on to extensive glomerular hyalinization with obliteration of capillary loops the blood pressure rises and pronounced hypertension may develop Contrary to the generally held opinion accepted in the previous editions of this book such evolution of hypertension does not necessarily signify that a nephrotic syndrome is due to glomerulonephritis (p 465) With hypertension the previously unchanged heart hypertrophies

Renal Function —Corresponding to what the histological findings would lead one to anticipate renal function is excellent in chronic nephrosis in children and in adults prior to the development of extensive glomerular hyalinization The urine is of high specific gravity even after allowing for protein the color is correspondingly deep the acidity is high and the urea content may exceed 3 per cent Azotemia is absent in fact blood urea nitrogen of less than 10 mg per cent is common in nephrotic children Phenolsulphonphthalein is promptly excreted The concentration test shows ability to form urine of specific gravity over 1 030

Glomerular filtration is not only unimpaired but the important studies of Emerson and his coworkers[145] have shown that it is often supernormal In 14 of their 33 nephrotic children under the age of ten years the urea clearance exceeded 140 per cent of the average normal one of them had a urea clearance of between 200 and 300 per cent for six years Supernormal

urea clearances were not observed in patients over eighteen years of age. Since Emerson *et al* found that the high urea clearance accompanied correspondingly increased renal blood flow (diodrast clearance) and glomerular filtration (inulin clearance) they concluded that the increased urea clearance in nephrotic children is due to augmented renal blood flow. That the increased filtration is not purely a consequence of decreased colloid osmotic pressure of the hypalbuminemic plasma is shown by Emerson's observation that it may persist long after the plasma proteins return to normal. And O'Leary and Corson[146] have found that renal blood flow and glomerular filtration change little when the plasma proteins of dogs are diminished by plasmapheresis.

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The *liver* is often palpably enlarged in nephrotic children. Fatty vacuolar and other regressive changes may be found histologically (Block *et al.*,[9] Blackman[17]), most often these alterations are slight. Gottfried and his associates[67] found that the thymol turbidity and cephalin flocculation tests often give abnormal results in nephrotic children but sulfobromphthalein excretion are normal and alkaline phosphatase values are not elevated. In adults, Boyd[151] found no evidence of damage to hepatic function in the nephrotic syndrome with the cephalin flocculation and thymol turbidity tests, the serum bilirubin and the urinary urobilinogen. The liver damage is not severe and hardly clinically significant. It may well be secondary to the hypalbuminemia for Elman and Heifetz[15] found that the hypalbuminemia of dogs on protein deficient diets is associated with vacuolization of the liver cells. There is no evidence that damage to the liver is responsible for the hypalbuminemia of nephrosis; the high content of the plasma in fibrinogen, which is also formed by the liver, bespeaks no diminution in the ability of the liver to synthesize protein.

Generalized *skeletal decalcification* was observed uniformly in nephrotic children by Emerson and Beckman.[153] Their x-ray studies revealed that the rarefaction is confined to the diaphysis, while the epiphyseal lines exhibit normal density. The children grow normally and have no evidences of rickets or other skeletal abnormality. Emerson and Beckman attribute the rarefaction of the shafts of the bones to the abnormally great loss of calcium in the feces which they demonstrated. Calcium is almost absent from the urine; this is presumably a result of the low calcium content of the blood.

On rare occasions, even in children, symptoms due to arterial or venous *thrombosis* occur. In Schwarz and Kohn's[33] patient, thrombosis of a cerebral artery caused sudden death.

Secondary Infections.—Patients with chronic nephrosis are very susceptible to infections. This may be correlated with diminution in antibodies included in the gamma globulin fraction of the plasma (p. 472). By taking repeated blood cultures, Schwarz and Kohn[33] were able to demonstrate bacteriemia at one time or another in 6 of 9 children with chronic nephrosis. In most instances the organism was pneumococcus Type IV but hemolytic streptococci were also grown on several occasions and pneumococcus Type III in one patient. Invasion of the blood stream occurred in one of their patients on four different occasions, three times with pneumococcus Type IV and once with hemolytic streptococcus. We have already mentioned that the most frequent portal of entry of the infection is probably the respiratory tract. Especially in children the clinical manifestations associated with bacteriemia in chronic nephrosis may be comparatively mild and the fever last only a few days. Schwarz and Kohn observed two clinical pictures in this type of case. In the one, the symptoms were peritoneal with abdominal pain, vomiting, distention, rigidity and tenderness, also present on rebound; all of these symptoms cleared up within a few days. Some of their patients had a number of such attacks. In the other children with positive blood cultures the manifestations were those of an upper respiratory infection with exudate often present on the uvula or rhino-pharynx.

Nephrotic Crises — Before penicillin transitory episodes of peritonitis with fever were common in nephrotic children (less so in adults) with ascites and are still occasionally seen. They may be recurrent. Pneumococci or other bacteria may be demonstrable in the peritoneal fluid or blood. Formerly such episodes most often subsided spontaneously but in other cases they went on to dangerous or even fatal peritonitis. With antibiotics they are now almost always quickly overcome and rarely occur in children kept on prophylactic doses of penicillin. Farr[184] and Emerson and Van Slyke[185] designated such episodes as "nephrotic crises." They found that the free alpha amino acids of the blood are lowered during the nephrotic crisis and that this lowering as well as a negative nitrogen balance may precede the fever and peritoneal signs. The Rockefeller investigators consider the possibility that the hypoaminoacidemia and negative nitrogen balance may bespeak a metabolic disturbance that lowers resistance and thus prepares the soil for organisms carried by the patient. MacLeod and Farr[186] found that the organisms invading the blood stream during the nephrotic crisis are those previously present in the patient's throat. Observations on the relations of the usually depressed gamma globulin content of the blood to the nephrotic crisis would be interesting.

In many cases these metastatic infections are not so mild and there may develop fatal peritonitis or bronchopneumonia. Before the introduction of sulfonamides and penicillin pneumococcus peritonitis was probably the most common cause of death in chronic nephrosis. The peritonitis seems to be due to infection of preexistent ascites. Usually the peritonitis is diffuse but it may be localized; pneumococci are generally found in spreads but may be difficult or impossible to grow. The onset may be as in the mild episodes just described but the fever then rises and the rigidity, vomiting and peritoneal facies become more marked. In other cases the clinical picture is severe from the very onset; one such patient was considered to have a perforation of the appendix and was operated upon under this diagnosis. Abdominal puncture and examination of the spread for pneumococci may establish the diagnosis in doubtful instances. In pre-sulfonamide days cases with severe symptoms of generalized peritonitis which did not improve within two or three days generally succumbed whether or not they were operated upon. However they sometimes improved. I saw this twice in adults and Schwarz and Kohn, Fanconi[17] and others reported recoveries in children in whom such a favorable termination was more common than in adults. Since sulfonamides and especially penicillin have been available the course of pneumococcus peritonitis has been completely changed; almost all the cases quickly respond.

Other infections may also occur. Schwarz and Kohn observed in a number of their children an erysipeloid lesion of the skin which lasted a few days; in one case an abscess formed from the pus of which they cultured a pneumococcus. The lesion occurs most often on the abdomen and thighs but may appear elsewhere; it may be very transitory or last over a week and is generally accompanied by fever. Erysipeloid is apt to recur. I have seen fatal erysipelas following subcutaneous drainage. Stolz[31] cultivated pneumococci from a pleural effusion and Munk[183] the same organism from an abscess in the myocardium. Bronchopneumonia was formerly a common cause of death. But nowadays these infections like pneumococcus peritonitis generally respond promptly to penicillin.

Recurrent Chronic Nephrosis.—Derow[159] has described a case in which the nephrotic syndrome recurred three times in fifteen years. Between the episodes, the patient was without albuminuria, edema, hypalbuminemia or hypercholesteremia; all of these were present during the recurrences. What seem to be similar cases were described by Addis.[160] Recently, I saw a child of four years with lipoid nephrosis in whom a ten day course of ACTH was followed by complete remission; after seven months of negative urine, for no apparent reason, the proteinuria and then the edema recurred.

III. DIAGNOSIS OF CHRONIC NEPHROSIS

The chief diagnostic problem which arises is the differentiation of chronic nephrosis from the other diseases in which the clinical picture is characterized by copious proteinuria and severe edema, namely, the nephrotic type of glomerulonephritis, diabetic glomerulosclerosis and amyloidosis.

The decision whether a patient suffers from the nephrotic type of glomerulonephritis or chronic nephrosis is often very difficult. Of course the definite history of onset with acute glomerulonephritis (hematuria, hypertension following scarlet fever, etc.) decides for chronic glomerulonephritis, but this is absent in many instances of the disease. Cases of glomerulonephritis may present for many months or years a clinical picture which simulates in every detail that of chronic nephrosis. There may be insidious onset, great edema, normal blood pressure, intact renal function, normal retina, marked proteinuria, doubly refractile lipoids in the urine, absence of hematuria and the nephrotic blood picture. It is such cases in which the clinical diagnosis of chronic nephrosis has been made and which are found at necropsy to have chronic glomerulonephritis that have caused some to be skeptical of the existence of chronic nephrosis. Prior to the age of five years chronic nephrosis is much more common than chronic glomerulonephritis. In later childhood and adult life up to the age of about sixty the reverse is true. In the aged, the proportion of nephrotic syndromes due to chronic nephrosis is higher. The presence of even a few red cells in the urine or the development of renal insufficiency or hypertension have often been regarded as conclusive evidence *that a patient* has glomerulonephritis. However, a small number of erythrocytes (less than 10 per high power field) in some of many examinations is common in nephrosis, and on rare examinations the urine of children ultimately proved anatomically to have chronic nephrosis exhibits many more erythrocytes. And in long standing lipoid nephrosis hypertension and renal insufficiency may result from hyaline obliteration of many glomerular loops. In my experience, however, this has occurred only after years of a nephrotic syndrome uncomplicated by hypertension or impaired renal function; cases in which the nephrotic syndrome evolves *pari passu* with hypertension and/or renal insufficiency have glomerulonephritis. There are many instances of the clinical nephrotic syndrome in which *intra vitam* differentiation between chronic nephrosis and glomerulonephritis is not possible. The writer would like to repeat that in his opinion the pendulum has swung too far toward the diagnosis of glomerulonephritis in the nephrotic syndromes of the elderly; many of these show at necropsy glomerular hyalinization with no evidence of antecedent glomerulonepritis

The differentiation of amyloid nephrosis from chronic nephrosis may also present difficulties. Usually, however, the presence of a cause for amyloid disease such as tuberculosis, long-standing syphilis or chronic suppuration settles the diagnosis. Or there may be other evidences of amyloid disease, such as enlargement of the liver and spleen or persistent diarrhea. But even if such evidence of amyloidosis of other organs cannot be detected clinically, a nephrotic picture in the presence of a cause for amyloid disease is almost always due to amyloid nephrosis. The Congo red test (p. 523) may be of value in the differentiation of amyloidosis from chronic nephrosis or aspiration biopsy may be conclusive (p. 526).

Chronic nephrosis occurring in the secondary stage of syphilis usually presents no diagnostic difficulties. If mercury has been given, the question arises whether the proteinuria is not due to the drug. If there is marked edema, it may be confidently stated that this is not due to mercury, and the indication is to continue the antisyphilitic treatment. According to Munk, doubly refractile lipoids do not appear in the urine in renal injury due to mercury; to be sure, they may also be absent in mild cases of chronic nephrosis. If the proteinuria disappears under antisyphilitic treatment, the question is, of course, settled.

Occasionally, especially in infants and young children, there may be some difficulty in differentiating chronic nephrosis from edema due to malnutrition. The examination of the urine will generally decide. In edema due to malnutrition there is generally no or but slight proteinuria, and the urinary volume may be normal or even decidedly increased despite the presence of edema. The changes in the blood proteins are similar in both conditions, but in nutritional edema there is generally a normal or low cholesterol content of the blood. In this connection, however, it should be remembered that in cachectic patients with chronic nephrosis lipemia may also be absent, though this is very rare.

THE PROGNOSIS OF CHRONIC NEPHROSIS

Some of the cases in which a diagnosis of chronic nephrosis is made after prolonged observation ultimately recover. The prognosis has improved since the introduction of sulfonamides and penicillin and perhaps even more with the use of cortisone and ACTH, but even in pre-antibiotic days there were many recoveries. This was particularly the case in children, in whom Holt and Howland lost only 2 of 20 cases, both of pneumococcus peritonitis and pneumonia. On the other hand, Schwarz and Kohn lost 5 of 9 children with chronic nephrosis. Later they reported that of 40 children with lipid nephrosis studied during a period of twenty years, 22 succumbed. Of 40 nephrotic children observed by Block et al.,[9] during a fifteen year period, 26 are alive, 19 have been entirely well for one to sixteen years, 3 have been well for less than a year and 4 still have the disease. Adults with chronic nephrosis, at least in my experience, do not do nearly as well. Contrary to most clinicians treating adults, Epstein is of the opinion that chronic nephrosis is a relatively benign disease, a high proportion of cases of which should recover if properly treated. On one occasion Epstein demonstrated 13 cases which had recovered. Schreyoegg...

reported 4 cases of chronic nephrosis in adults which recovered completely after illnesses lasting from one to ten years; in 4 of his other patients there remained only asymptomatic proteinuria. I have seen only a few recoveries from chronic nephrosis in adults. In 2 patients who got well proteinuria had been present for about ten years. In the recoveries that I have seen in adults the proteinuria was almost always discovered incidentally and the patient had little or no edema, although changes in the plasma proteins and lipids characteristic of the nephrotic syndrome were present. Of course, in the patients who recover the question of the certainty of the differentiation from chronic glomerulonephritis arises. I have not seen recovery in chronic nephrosis setting in after the age of forty. In most instances the disease is very protracted, dragging out over months and years, with periods of remission and exacerbation. Perhaps no disease is more trying to the patience of patient and doctor alike. Even when slight proteinuria is the only remaining evidence of the disease, there is always danger of a relapse. In some cases the edema clears up but the patient remains with proteinuria for years (thirty-two years in one case) while he is able to continue at his work. Or the patient may have periods of slight edema which do not inconvenience him notably.

In former years the chief cause of death in chronic nephrosis was infection, notably pneumococcic and other varieties of peritonitis, bronchopneumonia and pneumococcic or streptococcic bacteremias; erysipelas was a danger notably after subcutaneous drainage. The incidence and mortality of these infections has diminished greatly since the introduction of sulfonamides and antibiotics.

Paradoxically enough, intercurrent infections, notably with measles, may be followed by improvement (p. 492).

In adults, after a varying number of years which may extend to decades, hypertension and impairment of renal function may develop and the patient succumb to uremia or some cardiac or cerebral manifestation of hypertension and arteriosclerosis. As indicated above (p. 465) this course results from glomerular hyalinization.

The cases occurring in the secondary stage of syphilis usually respond to antisyphilitic treatment, though it may take a long time before the protein disappears completely from the urine. There are cases of chronic nephrosis complicating secondary syphilis in which antiluetic treatment is of no avail. In one such case reported by Dieulafoy the edema persisted and death from erysipelas occurred on the forty-fifth day. I have also seen a case of this kind in which antiluetic treatment did not help and when subcutaneous drainage was attempted fatal erysipelas ensued.

THE TREATMENT OF CHRONIC NEPHROSIS

Apart from the now almost extinct syphilitic cases there is no specific etiologic treatment for chronic nephrosis. The main measures in use are:

1. Sodium restriction.
2. Correction of protein starvation.
3. Intravenous infusion of plasma or serum albumin.

4 Administration of ACTH or cortisone
5 Prevention and treatment of intercurrent infections

Sodium Restriction — As in all edematous states sodium restriction is fundamental in the treatment of chronic nephrosis Often although not always reduction in sodium intake is followed by diminution in edema and aggravation results from increase in the sodium ration A low sodium diet is indicated in almost all nephrotic patients with edema During edema-free periods *more salt may be allowed if the patient craves it* But he should then be weighed daily and salt curtailed with any gain in weight. Care should be taken to avoid excessive sodium depletion especially during hot weather or considerable physical exertion Details of sodium restriction are discussed in the section on treatment of edema (p 174)

While sodium restriction constitutes one of the cornerstones in the management of nephrotic edema *Osman*[?] long ago pointed out that diuresis sometimes follows the administration of large doses *of mixtures of alkaline* salts Schlutz and Colver[?] reported excellent results in chronic nephrosis in children from heroic doses of alkali (starting with 8 grams and increasing to 30 grams daily of an equal mixture of sodium citrate and bicarbonate and potassium citrate and bicarbonate *in a syrup*) In recent years this method of treating edema has been extensively studied and advocated by Fox and McClune[?] who gave children daily *in one molar solution by* mouth [illegible] to 15 grams each of sodium and potassium acetates (acetate is a precursor *of bicarbonate*) Fox believes that the diuretic action of sodium and potassium acetates *in nephrosis is due to rectification* of abnormalities in the electrolyte economy—including lowering of sodium and bicarbonate in the *plasma and retention* of chloride and depletion of potassium in the *cells*—resulting from deficient renal *regulation* and that with this correction lowered plasma volume glomerular filtration and renal excretion of sodium and water are *augmented* The mechanism of the diuresis that occasionally follows the administration of large quantities of sodium and potassium acetates is not clear to the writer Some *special* constellation of the electrolytes must be present for *more* often in nephrotic patients diuresis is not produced by large doses of sodium and potassium salts and frequently the edema increases

The *water intake* should be regulated by the thirst *of* the patient unless there is dehydration or vomiting necessitates *parenteral fluids* (p 172)

Correction of Protein Starvation. —The treatment of *chronic nephrosis* apart from the syphilitic case revolves primarily about the regulation *of* the diet Formerly *the dietetics* of chronic nephrosis was much the same as that of other varieties of *Bright s disease* rigorous restriction of *protein* being generally *practised* * But the *brilliant* investigations of Epstein changed then prevalent views of the proper regimen *in chronic* nephrosis and *it has* been widely realized that not only is protein *restriction* not beneficial in this disease *but that* on the contrary it is very often detrimental for the following reasons

1 Patients with copious and *protracted* proteinuria need sufficient *protein* to replace not only the tissue protein *broken down* in metabolism

* It is however interesting that almost a century ago *the* eminent French clinician Piorry[?] who *introduced* mediate percussion and the plessimeter attempted to compensate for the albuminuria and combat the dropsy of Bright s disease by a high protein diet He gave 100 to 150 grams daily of white of egg He failed completely and even his attempt was forgotten

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content of the diet and not to the concomitant sodium restriction Theoretically, there are several ways in which augmenting the protein ration might help to reduce edema

1 Epstein originally believed that clearing of edema on high protein diet is partially due to rise in the plasma protein level However Maclean[166] and Wordley[167] soon observed patients in whom the high protein diet was beneficial although there was no rise in plasma albumin I have also seen many cases in which edema decreased greatly when the protein intake was elevated from a low level to 100 grams or more daily without concomitant change in the plasma albumin level But in other patients increasing dietary protein is followed by gradual though slow rise in plasma albumin In most of the cases in which there seemed to be definite correlation between elevation of protein intake and rise in plasma albumin there has been previous protein deficit because of either poor appetite gastro-intestinal disturbances or the prescription of a protein poor diet My impression is that apart from such cases in which protein intake was previously very low the plasma protein level in the nephrotic syndrome is primarily determined by the permeability of the kidneys to protein and that with massive proteinuria it is difficult indeed often impossible significantly to raise plasma albumin by dietary means It is not surprising that rise in plasma albumin actually due to higher protein intake is at best a low one The albumin of the plasma is in dynamic equilibrium with albumin located outside of the blood vessels and changes in the level of one component of the exchangeable albumin pool are doubtless paralleled by alterations in the other * And even when plasma albumin ascends *pari passu* with increase in protein intake it is difficult to be sure that the rise is actually due to dietary change fluctuations in plasma albumin level of obscure origin are common in the nephrotic syndrome even when dietary protein is constant Despite this well established fact there would seem no room for doubt that a high protein diet tends to facilitate regeneration of plasma proteins This is indicated by the recent finding of Adams and Figueroa[169] that while normals on an ample protein intake have very high capacity to regenerate plasma proteins removed by plasmapheresis such compensation is incomplete with lower protein intake

2 Maclean and Wordley suggested that reduction in edema on high protein diet is due to diuretic action of urea formed from the protein This may well be a contributing factor but the amount of diuresis observed from the therapeutic administration of corresponding quantities of urea in nephrotic patients indicates that it is not the only one

3 Epstein believes that another factor in the favorable effect of high protein diet is the specific dynamic action of the protein which in his opinion helps to counteract the occasionally low basal metabolic rate

4 In individuals suffering from protein starvation as a result of proteinuria and/or low protein intake increase in dietary protein may favorably affect anemia and general nutrition and thereby through mechanisms not clearly understood combat edema

* By the isotope dilution principle using I tagged albumin Sterling[168] found that the exchangeable albumin pool of healthy male medical students contains 259 ± 40 gram which is approximately equally distributed between the intra and extravascular locations

but also the protein lost in the urine Children also need ample protein for growth As was seen above, the loss of highly differentiated plasma protein in the urine may amount to 20 or 30 grams a day over a period of months

2 The concentration of albumin in the blood plasma is lowered in chronic nephrosis, which is the primary cause of the edema it would seem probable that a large quantity of protein in the diet facilitates regeneration of the plasma proteins

3 Chronic nephrosis is a disease which extends over months or years restriction of protein for such long periods renders the patient weak anemic and presumably more susceptible to the secondary infections that are his chief danger

It was to meet the above indications that Epstein broke completely with tradition and introduced his *high-protein diet* Following initial opposition because of the traditional fear of both physicians and the laity of meat and other protein foods in Bright's disease Epstein's contention that very considerable quantities of protein should be supplied the patient with chronic nephrosis has been very widely accepted though there is still a diminishing number of opponents *e g* Addis [1] And in actual practice it seems quite clear that better results are obtained by giving the patients ample protein This is often demonstrated when patients whose protein intake has previously been severely restricted are given an ample ration of protein they regain strength feel more hopeful the anemia improves and the edema may decrease or even disappear That these patients actually suffer from protein starvation seems to be shown by a careful metabolic study of cases of the nephrotic type of glomerulonephritis and chronic nephrosis by Peters and Bulger [164] who find that If they are given more than enough protein to replace the amount lost in the urine, they will store the excess within certain limits thus repairing the effects of the previous nitrogen wastage In one of their cases the storage lasted for almost three months A similar retention of nitrogen has been observed by Peters and by Grabfield [165] to follow the administration of large quantities of crystalline urea to a nephrotic patient Inasmuch as Grabfield found that the *nitrogen retention was accompanied by sulphur retention* and did not result in elevation of the non protein nitrogen of the blood he suggests the possibility that the nitrogen of the urea may be built up into deposit protein to replace that which has been lost as a result of the proteinuria If this interpretation is correct and the evidence for it is at least very suggestive it is of far reaching general metabolic significance Moreover it would indicate that the administration of large quantities of urea to nephrotic patients is of value not only as a diuretic but also to help in the regeneration of the lost protein However further evidence is needed before this conclusion can be drawn

In former years when most patients with edematous forms of Bright's disease were kept on a protein poor diet it was common to observe diuresis and disappearance of edema when an adequate protein ration was instituted Nowadays since the dangers of protein starvation in massive proteinuria are generally appreciated it is exceptional to see striking benefit which can be unequivocally attributed to increasing the protein

Subsequent investigations showed that nothing is gained by raising the protein intake to very high levels. Peters and Bulger found that by the administration of large amounts of carbohydrate and fat to patients with the nephrotic syndrome they reduce the daily protein catabolism to from 0.5 to 0.7 gram per kg body weight. If this is done a daily ration of about 100 grams of protein furnishes a large surplus over the amount catabolized plus that lost in the urine. In protracted observations on patients with the nephrotic syndrome Liu and Chu[150] found that maximum protein storage was obtained with 2.5 grams of protein per kg body weight in a boy aged ten years and with 1.8 grams in an adult; this protein ration supplied 12 to 13 per cent of the total calories. One of their patients showed a slightly greater nitrogen storage when higher percentages of the protein were of animal origin while in the other the nature of the protein made no distinct difference. In accord with the above mentioned findings of Peters and Bulger, Keutmann and Bassett[49] found that with a given protein intake increasing the calorie value of the diet by increments of carbohydrate and fat augmented the deposition of protein.

From these observations it would appear that there is hardly any advantage in feeding more than 100 grams of protein daily to an adult with chronic nephrosis provided there is no fever and the caloric content of the diet is high. Under these conditions I no longer give larger quantities of protein; very high protein diets are often difficult for the patient to take. Because of growth requirements children require relatively higher protein rations than adults. However Farr[1 7] found that even children fail to assimilate more than 3.3 grams of protein per kg body weight. His observations indicate that the optimum protein intake for nephrotic children is but little above that of the healthy child. There seems to be no evidence that any advantage accrues from giving children with the nephrotic syndrome more than 2.5 grams of protein per kg body weight.

The diet should contain sufficient carbohydrate and fat to give it a high caloric value and thereby decrease protein catabolism. In general the patients find a diet relatively high in carbohydrate easier to take. Epstein originally recommended a fat poor diet to combat the lipemia. He found however that the elimination of fatty food from the diet does not notably influence the lipemia of chronic nephrosis. This has been confirmed by Page and Farr.[1 8]

Nor is there any evidence that the lipemia is harmful (apart from possibly causing some atherosclerotic changes) and the fat may be a very valuable source of energy. There is therefore no objection to the use of considerable quantities of fat in the diet.

The most generally helpful diet in chronic nephrosis would thus seem to be one containing about 100 grams daily of protein and of high caloric content from both carbohydrate and fat. Sodium is restricted as much as is compatible with adequate protein intake. Often sodium poor protein hydrolysates are of great aid in attaining the twin goals of low sodium and high protein intake. During edema free periods the patient may gain too much weight from the high carbohydrate and fat content of the diet and these sources of energy may have to be restricted. All the arts of the kitchen must be used to render the diet palatable or even tolerable to patients

5 There is still another mechanism, hitherto hardly considered through which augmentation of the protein content of the diet may enhance diuresis, namely, *increase in blood flow through the kidneys* Jolliffe and Smith[170] showed that in the dog urea clearance is greater on a high than on a low protein diet, and it has since been found in the same animal that glomerular filtration and renal blood flow are both accelerated by high protein diet (Van Slyke *et al* [171] Pitts[172]) While in man these differences seem not to be as great there is also evidence that glomerular filtration and renal blood flow are both more rapid on a high protein diet than when dietary protein is low (White and Rolfe,[173] Pullman *et al* [174]) That increased protein content of the diet calls forth greater renal work is shown by the hypertrophy that it produces in the rat's kidney (Addis[175]) These findings indicate that increase in dietary protein has a profound augmenting effect on renal blood flow and function, which may be important when diuresis is produced on such a diet

It would appear that the relations between variations in the protein content of the diet and the urinary volume in nephrosis are complex and not well understood

Hypothetical objections may be raised to an ample protein diet in chronic nephrosis In rats with experimental nephritis (p 558) or subjected to ablations of large parts of the kidney (Addis[176]) it has been found that high protein diets may accelerate renal failure And to the extent that increase in the protein content raises the plasma albumin level there will be an increase in the proteinuria that may be damaging to the kidneys But there is no evidence that either of these deleterious effects occurs in lipoid nephrosis

√*Before increasing the protein content of the diet one must be certain that renal function is intact* √Any evidence of impairment of renal excretory function immediately contraindicates the high protein diet although it does not militate against an adequate protein ration (*e g* 50 grams plus the loss in the urine daily) The specific gravity of the urine should be watched carefully throughout the course of the disease If the concentration test (p 95) shows that the specific gravity can exceed 1 022 there need be no fear of serious nitrogen retention even if the urinary volume is as small as 500 cc daily Not uncommonly there will be a rise in the urea nitrogen content of the blood to about 25 or 35 mg per 100 cc during the high protein diet but this need occasion no fear as long as the high specific gravity of the urine shows that renal function is good As Maclean Peters and Bulger and others have pointed out there is no convincing evidence that moderate increase in the nonprotein nitrogen of the blood is in any way harmful

The diet originally recommended by Epstein is as follows Protein 120 to 240 grams fat 20 to 40 grams and carbohydrate 150 to 300 grams having an energy equivalent of from 1250 to 2500 calories He allows from 1200 to 1500 cc of fluid daily and sufficient salt to make the diet palatable The articles of food used by Epstein are lean veal lean ham whites of eggs oysters *gelatin lima beans, lentils split peas green pea* mushrooms rice, oatmeal, bananas skimmed milk coffee tea and cocoa

shown by catheterization of the renal vein that renal blood flow is greatly increased and there is marked acceleration of glomerular filtration. However, decreased tubular reabsorption through endocrine mechanisms may also enter (Luetscher).

The diuresis from a single injection of even 50 or more grams of salt-poor albumin is transitory, and to obtain significant results the injection must be repeated a number of times. The diuresis usually stops soon after the termination of the injections; further continuation is probably due to an alteration in the spontaneous course of the disease. Following Thorn's technique, salt-poor albumin is generally given in 10 per cent solution containing 6 per cent of glucose at a rate of 100 cc. per hour. In adults 50 grams may be given daily, in children 10 to 25 grams. Thorn found that doses above 50 grams daily are not proportionately more diuretic.

The value of salt-poor albumin in chronic nephrosis has not proved to be as great as originally hoped for. Usually, but by no means always, it is possible by repeated injections to reduce the edema considerably or even completely. But diuresis generally stops with cessation of the injections and the edema usually returns unless there is spontaneous remission. The chief benefit from salt-poor albumin is in extremely edematous patients who do not respond to other measures; in them, if a brief period can be tided over with the aid of albumin, spontaneous remission may set in or salt restriction or other treatment may maintain the improvement. No good purpose would seem to be served by administration of salt-poor albumin to patients with little or no edema; actually, in these circumstances little diuresis is usually produced. Salt-poor albumin is very dear and many patients have gone to unjustified expense where little benefit was to be anticipated. There is no reason to believe that administration of albumin has more than a temporary effect or that it alters the natural history of nephrosis. It should not be given in the presence of marked hypertension or renal insufficiency for fear that the sudden expansion of blood volume will overstrain the heart; pulmonary edema of this mechanism has occurred. Not rarely patients complain of difficulty in breathing or fullness in the head during the injections.

Acacia. – Acacia is a colloid which leaves the blood stream but slowly and while there elevates the oncotic pressure of the plasma. It may still be found in the blood stream three years after injection. Used as a plasma expander in the treatment of shock in World War I, it was introduced into the treatment of nephrotic edema by Hartmann[187] and was later advocated by Landis,[188] Binger[189] and others. Hartmann gave about 1 gram of acacia per kilogram body weight. Acacia is obtainable commercially in 30 per cent solution containing 1.5 per cent of sodium chloride. Hartmann and his associates observed good results when they administered this 30 per cent solution diluted with an equal volume of distilled water. In severe cases with nephrotic edema the injection has to be repeated every three or four days to maintain an effective concentration in the plasma. They administered acacia to 6 patients with chronic nephrosis. In 5 of the 6 patients diuresis was produced whenever sufficient acacia had been taken to bring the colloid osmotic pressure of the serum up to between 13 and 21 cm. of water. By continuing the administration long enough they were

with poor appetites, but this can usually be accomplished The technique of sodium restriction is discussed in Chapter 6

Intravenous Infusion of Plasma and Serum Albumin —Attempts were long ago made to elevate the lowered oncotic pressure of the plasma and repair the protein deficit of chronic nephrosis by transfusion of blood or plasma Apart from improvement of anemic patients by blood transfusion, the results were doubtful and at best transitory enough protein significantly to affect the enormous deficit could hardly be obtained from unconcentrated plasma Much better results were gotten by Aldrich and his coworkers[1, 9] by infusion of human blood serum concentrated five times by the lyophile process In 6 of 9 children with chronic nephrosis they observed immediate diuresis with clearing of edema followed the injection The preparation of concentrated serum albumin during World War II by the Harvard Plasma Fractionation Laboratory and especially of salt poor albumin (Scatchard *et al*[150]) offered a promising method for combating hypalbuminemia and protein deficiency in the nephrotic syndrome Clinical trials of albumin in the nephrotic syndrome were soon made by Janeway[151] Luetscher[152] Thorn[153] and their associates and it has since been widely used though the great expense has been a drawback

When albumin is injected intravenously into an individual with edema the increased colloid osmotic pressure of the plasma draws remarkably large volumes of intercellular fluid into the blood stream * Luetscher found that the injection of 50 grams of salt poor albumin might be followed by a rise in plasma volume of as much as 50 to 100 per cent with visible venous distention and rise in venous pressure The amount of the rise in plasma albumin concentration and oncotic pressure is largely determined by the extent of the dilution of the blood by tissue fluid The concentration of globulins generally falls because of dilution of the blood Unfortunately the increase in circulating albumin produced by the injection is transitory it is quickly distributed between the plasma and the extravascular compartment of the protein pool and much is lost in the urine If the albumin level in the plasma is built up by repeated injections the proportion of the injected albumin lost in the urine rises because of increased filtration Luetscher found that at the end of two weeks after a course of albumin injections all the albumin given can be accounted for as excess albumin and nonprotein nitrogen in the urine

Injection of albumin into an nephrotic patient with edema is followed by water diuresis of varying magnitude In nonedematous individuals without a large volume of intercellular fluid available for osmotic mobilization diuresis is slight or absent ** Luetscher found that when increased excretion of sodium is produced by injection of albumin it follows the water diuresis if no rise in sodium excretion occurs water diuresis also stops The mechanism of the diuresis is not entirely clear Cargill[156] has

* According to the calculations of Scatchard Batchelder and Brown[154] each gram of albumin should hold about 18 cc of fluid in the blood stream

** In fact Petersdorf and Welt[155] found that in normals hyperoncotic solutions of albumin have an antidiuretic effect due to increased tubular reabsorption of water which they regard as a passive consequence of enhanced reabsorption of sodium chloride in the proximal convoluted tubule

to children and 300 mg to adults There seems to be no advantage in increasing the dose and it may be that smaller amounts are equally effective Inasmuch as diuresis is most apt to appear to occur after cessation of cortisone or ACTH even as long as four days after the hormone should be given in a course which is terminated abruptly without tapering off There appears to be no greater likelihood of obtaining a satisfactory response by prolonging the course to more than ten days If the result is unsatisfactory a second course may be given after five days Sometimes diuresis is first obtained after a second or even third course Diuresis may be produced during repeated courses

Recently Lange[198] and his associates have obtained remissions of longer duration by intermittent administration of ACTH or ACTH followed by cortisone They gave 6 children with the nephrotic syndrome 100 mg of ACTH daily for seven days diuresis occurred in all between the ninth and twelfth days This was followed by 100 mg of ACTH daily for three consecutive days for the next five to eight weeks Only transitory relapse of edema occurred in 1 of the patients during an observation period of six to twenty six months In other cases Lange and his associates used oral cortisone (100 mg q i d) for three consecutive days for the interrupted treatment after the initial ACTH course This interrupted method of treatment has seemed effective to me but there are also relapses on it

While diuresis may set in at any time during the administration of the hormone this is usually preceded at least during the first days by retention of sodium chloride and water with resultant increase in edema and weight during this period there is often increase in proteinuria and perhaps in lipemia The urinary volume may then increase while the hormone is still being given However if a response is obtained at all the more frequent sequence is for diuresis to set in one to three days after ACTH or cortisone has been stopped and for urinary volume to remain at a high level for several days until the edema is largely or completely evacuated At the same time proteinuria may diminish or even disappear plasma albumin rise and plasma lipids fall *Farnsworth found that triglycerides may fall even though cholesterol is unchanged With diuresis a moderately elevated NPN may fall to normal Lowered plasma sodium may rise with the diuresis As mentioned above the remission is most often brief but may be protracted into months If the patient remains well it is still to be proved that this is due to the treatment and is not the natural course of the disease Continuous treatment over long periods of time with ACTH or cortisone has been tried (Kramer[2] et al Merrill[24] and Mitchell) but I have not yet used it the probabilities of undesirable and perhaps insidious side effects of such long term treatment have yet to be evaluated against possible benefits With small maintenance doses of cortisone (37 5 daily) over long periods Riley had relapses in 10 of 12 nephrotic children

Little definite is known concerning the mechanism of action of cortisone and ACTH in the nephrotic syndrome In normals Earle et al [90] found that ACTH increases the filtration rate and filtration fraction but decreases renal blood flow Levitt[201] also observed that the filtration rate and fraction are progressively increased during cortisone or ACTH therapy reaching their peak about the eighth or ninth day Correspondingly Selye's[202]

able completely to rid their patients of edema. When the first injection failed, a second one given within a day or two produced striking results. Landis advised that, after a test dose of 5 or 10 grams, acacia should be administered by slow intravenous injection in daily amount of 20 to 30 grams until 120 to 180 grams have been given. Using this technique, he obtained good diuresis in 5 of 6 patients with nephrotic edema. Because of the danger of severe reactions with chills and circulatory collapse with large doses, which I have seen repeatedly, such divided dosage is to be preferred. Austin and McGuinness[190] observed dangerous rise in blood volume following a large injection. I obtained excellent diuresis in several patients with nephrotic edema by the injection of acacia but in others it failed. Mercurials previously unsuccessful may produce diuresis after the colloid osmotic pressure of the plasma has been raised by acacia.

In addition to the acute reactions just mentioned, acacia has another undesirable by-effect: it is deposited in large quantities in the liver cells where it may remain for long periods. Yuile and Knutti[191] showed experimentally that the administration of acacia produces chronic hypoproteinemia. It appears that the deposition of acacia in the liver inhibits the formation of plasma proteins in this organ. For this reason acacia has been almost abandoned in recent years. I have not given it in several years.

The recently developed plasma expander, *dextran*, has also been tried in the treatment of nephrotic edema. Wallenius[8] found that each intravenous injection increased the urinary volume in the nephrotic syndrome by at least 400 cc. Oliver[9] *et al.* administered a 10 per cent salt free solution of dextran to 12 children with nephrotic edema in doses averaging 1.43 gm. per kilogram body weight. Diuresis was produced but the effects were temporary.

Cortisone and ACTH.—In some patients with the nephrotic syndrome remarkable diuresis and regression of edema is produced by ACTH or cortisone. *Clinical remission with disappearance of edema, diminution or rarely even disappearance of proteinuria, rise in plasma albumin and fall in plasma lipids may occur.* Diuresis is produced more often than diminution in proteinuria and may occur in the absence of the latter or significant change in plasma albumin level (Luetscher,[7] own observations). Usually the remission is of brief duration but it may last for months or in rare instances exceed a year. That hormonal therapy *per se* results in cure of chronic nephrosis has not been demonstrated. Luetscher[19] observed diuresis from cortisone in 6 of 11 patients with the nephrotic syndrome. Reports by Farnsworth and Dupee,[193] Luetscher,[194] Metcoff,[195] Spector,[19] Riley[196] and Rapoport[198] *et al.* indicate that corticotropin produces diuresis in one or more courses in about two thirds of nephrotic patients. In my experience the proportion has been even higher in the first trial in young children but lower in adults. In the cases personally observed ACTH has proved more frequently effective and has produced a more profuse diuresis than has cortisone. However, Riley found both agents equally effective.

In adults 75 to 100 mg. daily of ACTH may be given intramuscularly or a correspondingly smaller amount intravenously; in young children about 50 mg. daily is a usual dose. About 200 mg. daily of cortisone may be given

with lipoid nephrosis and 3 with the nephrotic form of glomerulonephritis who developed measles while in the hospital The disease subsided in the 2 children with lipoid nephrosis one was still well ten months later while the other relapsed after three and half months The 3 children with glomerulonephritis had only transient improvement When nephrotic children develop measles there may be aggravation of the nephrotic syndrome in the pre-eruptive stage with diuresis when the rash is florid Remission induced by measles may be complete with disappearance of proteinuria and edema and return of the plasma proteins and lipids to normal Unfortunately the remission generally proves transient when this is not the case, the possibility exists that there has been spontaneous cure While the mechanism of improvement following measles is obscure a relationship to the remissions induced by cortisone or ACTH comes to mind the defence mechanism may include hypersecretion of corticotropin

Improvement of the nephrotic syndrome may also be induced by other infections notably viral Thus Berger and Zoole[207] observed a six month remission following homologous serum jaundice

Because of the observations of remission following measles, the disease has been induced for therapeutic purposes in children by exposure or inoculation Janeway[181] inoculated 12 nephrotic children with measles Of these the a with lipoid nephrosis respond strikingly while only 3 of the 7 with glomerulonephritis had a good response There were no cures and the edema returned in one to six months Janeway carried out the inoculation by nasal instillation of throat washings from patients with Koplik spots which were treated with several hundred thousand units of penicillin and stored at minus 70 C Patients inoculated with measles should be given penicillin as a prophylactic of secondary infections

The remission of chronic nephrosis by measles seems to be akin to that resulting from ACTH For this reason and since the child may be very sick with measles induction of the disease for therapeutic purposes does not now seem advisable

Thyroid Extract —This has been extensively used in the treatment of chronic nephrosis

Eppinger[208] found that the resorption of salt solution from the subcutaneous tissues is slower than normal in the thyroidectomized animal He was able to accelerate greatly the resorption of the salt solution by the administration of thyroid extract In several instances of edema of obscure nature which had resisted other measures Eppinger induced diuresis and cleared up the edema by thyroid therapy Volhard[99] observed an excellent therapeutic result from the administration of thyroid in a case of chronic nephrosis

Large doses of thyroid and thyroxin were however first used extensively in the treatment of chronic nephrosis by Epstein from whose work dates the formerly wide utilization of thyroid treatment in chronic nephrosis He was led to its use by his observations of lower basal metabolism in many cases and by other analogies between the clinical pictures of myxedema and chronic nephrosis Epstein found that patients with chronic nephrosis have enormous tolerance for thyroid rarely manifesting any toxic symptoms or notable elevation in the basal metabolic rate as long

animal experiments revealed that large doses of ACTH produce dilatation and hyperemia of the glomerular loops Increase in PAH clearance and other evidences of improved tubular function have been observed by Metcoff *et al* Luetscher [93] found a decrease in the previously high urinary excretion of salt-retaining corticoids during diuresis from either cortisone or ACTH It appears that the respective roles of increased glomerular filtration and tubular rejection of water and salt in the diuresis induced by cortisone or ACTH have not yet been assessed

At present the use of ACTH or cortisone constitutes the most valuable therapeutic measure available for treatment of the nephrotic syndrome, even though it is not yet proved that the hormones influence the fundamental course of the disease They should be tried in patients who do not respond to salt restriction and high protein diet In the presence of massive edema not evacuated by other measures, ACTH or cortisone may be tried despite *slight* hypertension or azotemia and may produce diuresis However they should be used very cautiously under these circumstances and stopped if there is any rise in blood pressure or azotemia With marked hypertension the hormones should not be used for they may dangerously or even fatally aggravate the hypertension I have seen three patients with renal disease (two with glomerulonephritis and one who apparently had renal involvement in scleroderma) in whom the administration of ACTH was followed by dangerous hypertension none of these however, had a nephrotic syndrome In view of the lowered resistance of the nephrotic patient to infection it is probably wise to accompany the hormone by penicillin if there is active infection because it is possible that ACTH or cortisone may lower resistance the doses of the antibiotic should be large Metcoff *et al* mention three deaths in children with the nephrotic syndrome during treatment with ACTH (hypertension with hypotonicity and convulsions and overwhelming infections) which seemed to be related to the treatment Orange juice and/or potassium salts should be given to prevent hypokalemia and metabolic alkalosis Acne hirsutism moon face etc may occur during treatment but quickly pass away and are not deterrents Slight elevation of blood pressure is not rare I have seen 2 instances of massive hemorrhage from one adrenal gland during ACTH treatment for the nephrotic syndrome the first case was subjected to laparotomy because an acute abdominal catastrophy was suspected During the diuretic phase sodium or/and potassium depletion may occur and require administration of the appropriate ion Contrariwise Luetscher[225] points out that in early days of treatment marked hyperkalemia may occur

Infection With Measles —It was long ago observed that patients especially children with chronic nephrosis may have profuse diuresis following an intercurrent infection notably measles Debre [94] and his associates reported a case of nephrosis of four years duration in which measles was followed by remission of at least four months They collected 15 other cases with remission due to measles which was permanent in 2 Rosenblum *et al* [95] studied 7 children with the nephrotic syndrome who contracted measles during an epidemic Three had protracted and 3 permanent improvement Blumberg and Cassidy [96] observed 2 children

with lipoid nephrosis and 3 with the nephrotic form of glomerulonephritis who developed *measles* while in the hospital. The disease subsided in the 2 children with lipoid nephrosis: one was still well ten months later while the other relapsed after three and half months. The 3 children with glomerulonephritis had only transient improvement. When nephrotic children develop measles, there may be aggravation of the nephrotic syndrome in the pre-eruptive stage with diuresis when the rash is florid. Remission induced by measles may be complete with disappearance of proteinuria and edema and return of the plasma proteins and lipids to normal. Unfortunately, the remission generally proves transient; when this is not the case, the possibility exists that there has been spontaneous cure. While the mechanism of improvement following measles is obscure, a relationship to the remissions induced by cortisone or ACTH comes to mind; the defence mechanism may include hypersecretion of corticotropin.

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as the lipemia is present He observed that in many instances of chronic nephrosis, the use of thyroid extract diminishes the proteinuria, produces diuresis with reduction in the edema, and reduces the lipemia In Epstein s opinion these beneficial results are due to stimulation of protein metabolism and abnormality of which he regards as the fundamental basis of the disease Epstein uses thyroid therapy purely as an adjuvant to his high-protein diet, both serving to increase the utilization of protein Another factor that might be concerned when thyroid therapy is effective in chronic nephrosis is the increase in colloid osmotic pressure of the plasma proteins which Malkin[210] reported after the administration of thyroid, this observation has not been confirmed and seems improbable

Epstein starts with small doses of thyroid extract (0 5 to 1 grain three times daily) and then increases until 15 grains a day is reached In some cases he has given much larger doses or used thyroxin intravenously (5 to 10 mg repeated in a week) He has found that toxic symptoms do not develop as long as hypercholesteremia is present and uses this as a guide for the dosage In some instances he has persisted in thyroid treatment for over a year

While diuresis occasionally follows the administration of thyroid much more often there is little or none When definite diuresis does occur it is difficult to exclude spontaneous fluctuations in the disease And theoretically the advisability of accelerating protein metabolism in a disease characterized by protein depletion seems dubious The lowered basal metabolic rate when present after allowance for edema may be an adaptation to the protein deficiency The writer has not used thyroid in the nephrotic syndrome in several years apart from rare instances in which there seemed to be good evidence of hypothyroidism

Diuretics — *Mercurial diuretics* sometimes produce copious diuresis in the nephrotic syndrome This is more apt to occur after preparation with ammonium chloride or another acid producing salt (p 190) However, the mercurials are often totally ineffective in chronic nephrosis and when they are diuretic their efficiency generally decreases with successive injections It is rare to be able to control the edema of a severely hypoproteinemic patient with mercurials There seems to be little danger in chronic nephrosis from the cautious probatory use of mercurials by subcutaneous or intramuscular injection Saxl and Becker [11] found that the injection of salyrgan diminishes the quantity of protein in the urine in chronic nephrosis However I have seen augmented proteinuria and the appearance of red cell in the sediment following use of a mercurial in nephrosis If the first injection of a mercurial to a patient prepared with ammonium chloride does not produce diuresis it does not seem to be worth while to continue with the injections

Urea is a diuretic which is exceptionally helpful in controlling edema for months or even years Urea must be given in large doses (60 to 90 grams daily or even more in 50 per cent solution in syrup or in capsules) The disagreeable taste nausea vomiting or diarrhea often necessitate discontinuance

Purine diuretics are usually useless from the start or soon lose any effectiveness they may initially display

The use of large doses of *sodium and potassium* salts in chronic nephrosis has been mentioned above (p 483)

Cation Exchange Resins — These are occasionally a valuable adjuvant to sodium restriction in clearing the edema of the nephrotic syndrome. Lippman[22] obtained diuresis by use of a resin in 11 of 14 nephrotic patients and was able to maintain most of them virtually free of edema for periods up to one year. My results have not been nearly as favorable but in a few cases use of a resin has delivered edema. If there is impairment of renal function documented by hyposthenuria a cation exchange resin should be administered only with great circumspection: there is much danger of acidosis due to base depletion and sometimes hypokalemia develops. After a few days potassium chloride should be given. There is great difficulty in getting children (and many adults) to take a resin. Cation exchange resins should not be given to patients with azotemia because the likelihood of help is slight and the dangers of acidosis and hypokalemia great.

Other Measures — *Infectious foci* should be removed or drained but one should be cautious in predicting good results from the operation. In adults I have seen no striking if any benefit from *removal of tonsils, drainage of sinuses* etc. In view of the good results obtained by pediatrician by drainage of the paranasal sinuses in nephrotic clinical pictures these should be examined and treated by a specialist (see p. 484). However in my experience benefit that could be unequivocally attributed to such procedures has been decidedly exceptional. Nowadays treatment of sinus infection in nephrotic patients with other than by antibiotics is rarely called for.

On the basis of the rare instances in which improvement follows febrile infections (p. 492) treatment by *injections of foreign protein* has been tried but generally with little success. Clement[23] reported cure of chronic nephrosis in a fifteen year old boy following pyrotherapy by *injections of sulphurated oil and antityphoid vaccine*. Such improvement as is actually correlated with these measures if any is probably identical in mechanism with the diuresis following ACTH injection of the latter is more effective and certainly less trying to the patient.

Mechanical removal of edema may be necessary. Extensive effusions into serous cavities should be tapped if they cause dyspnea or other symptoms that do not respond to diuretic measures. Salt restriction may be more effective after tapping ascites. It is best to avoid drainage of the subcutaneous edema because of the extreme susceptibility of these patients to infection but in rare instances it becomes necessary and penicillin has almost eliminated the formerly great danger of erysipelas or cellulitis.

Decapsulation has been recommended in chronic nephrosis. Oehlecker[24] reported 2 cases in which this operation was followed by marked improvement. In view of the fluctuating course of so many of these cases it appears to me difficult to evaluate the benefit of the operation. There appears to be no rationale for the operation which I have not advised.

General Care — The question of how long the patient should be kept in bed may present difficulties. With massive edema or febrile complications there is no alternative to bed rest. But if the patient is comfortable while up and about despite increase of the edema of the legs toward evening there seems to be no good reason for enforcing bed rest. Small children are

best allowed to play throughout the home, and in mild weather outdoors, despite considerable edema and ascites The improved appetite while up and about facilitates adequate diet Many patients with proteinuria and low grade edema are able to pursue an occupation even though the feet swell more as the day goes on Of course every effort is to be made to avoid respiratory infections and protect children from contagion If circumstances permit and dietary control is possible, nephrotic patients may prefer to pass the winter in the South where they can be outdoors and the changes of respiratory infection are less But climatic treatment has no remarkable virtues in chronic nephrosis and a family should not be permitted to ruin themselves financially in order to obtain it

Antiluetic Treatment —In syphilitic nephrosis antiluetic treatment should be given and usually is curative Formerly mercury or bismuth (Felber) were the usual initial drugs, followed by arsenicals Overly energetic treatment with these drugs was observed to provoke Herxheimer reactions with anuria increasing azotemia edema and uremia (Moore [15]) At present penicillin is the drug of choice (Tucker [16])

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Chapter

17

DIABETIC GLOMERULOSCLEROSIS

It is now three decades since vascular disease has displaced acidotic coma as the great menace of the diabetic Among the organs most severely affected are the kidneys In 1917 shortly before the insulin era, Joslin[1] wrote presciently The renal complications of diabetes have been unimportant in the past but with the prolongation of life which modern treatment is bringing about they will deserve attention Vascular implication of the kidneys in diabetes differs from that in the heart, extremities and other organs in that it is the result not only of arteriosclerotic ischemia, but also includes a remarkable lesion in the glomerular tufts, of which the analogue in other organs (except perhaps the retina) has not yet been described

The attention of the profession was first drawn to the distinctive renal lesions of diabetes by the communication of Kimmelstiel and Wilson[2] in 1936 In 8 necropsies in 7 of which there was a history of diabetes, they observed characteristic hyaline nodules in the Malpighian tufts They believed these to arise from a hyaline thickening of intercapillary connective tissue in the glomerulus and therefore termed the lesion *intercapillary glomerulosclerosis* There was also lipoidosis of the tubules and inter tubular tissue They found that the clinical picture of patients presenting this lesion includes diabetes massive proteinuria nephrotic edema hyper tension and uremia This clinical and anatomical constellation has since often been referred to as the *Kimmelstiel Wilson syndrome*

More recent observations indicate that the characteristic glomerular lesions originate in hyaline thickening of the basement membrane of the glomerular loops rather than between them and that hyalinization of the afferent and efferent arterioles is also usually concerned in the genesis of the renal disease The process is an intrinsic part of the widespread degeneration of the vessels in diabetes The designation *intercapillary* is thus not wholly felicitous though it well describes the usual histologic appearance and we will more often speak of diabetic glomerulosclerosis

The clinical picture and anatomic findings first described by Kimmelstiel and Wilson occur so frequently* on every medical service that many physicians must like the writer have chided themselves for failure to discern their correlation with diabetes The frequency with which glomerulosclerosis develops in long-standing diabetes is now familiar to all intern

* On the Medical Service of Beth Israel Hospital where the proportion of diabetics tends to be high for an acute general hospital in recent years there have been more cases of diabetic glomerulosclerosis than of glomerulonephritis

ists Nevertheless, doubts have been expressed regarding the *specifically diabetic* causation of the renal lesions, in fact Kimmelstiel and Wilson originally regarded them as merely an intensification of a sclerotic process that commonly develops in the kidneys of the aged in the absence of diabetes Horn and Smetana[3] claim to have found the same renal changes more often in nondiabetics than in diabetics, although they observed the far advanced lesions only in diabetics Recent careful anatomic studies by Siegal and Allen[4] and Bell[5] have shown that the typical large spheroidal hyaline nodules in the glomeruli are almost but not absolutely pathognomonic for diabetes Siegal and Allen and Bell each mention a single exception in a nondiabetic and I recall very rare instances in which globular hyaline lesions were seen in the glomeruli of arteriolosclerotic kidneys where there was no evidence of diabetes But the rarity of such exceptions should be stressed Moreover if the full blown clinical picture—diabetes hypertension, marked proteinuria, nephrotic edema azotemia and above all diabetic retinopathy—is present, one can confidently predict that the hyaline glomerular lesions will be found In aglycosuric cases mild diabetes is sometimes detected as a result of sugar tolerance tests instigated by the presence of some of the clinical manifestations just enumerated

Occurrence —Glomerulosclerosis is a common development in present day diabetics In fact Lapply[6] *et al* detected the lesion at post mortem in a higher proportion of diabetics than had hyalinization of the islets of Langerhans Allen observed the lesion in one-third of diabetics over forty Henderson[7] *et al* found glomerulosclerosis in 61 of 313 autopsies on diabetics From a survey of the available statistics Kimmelstiel and Porter[8] conclude that glomerulosclerosis occurs in about 17 per cent of all diabetics twice as often in women as in men The peak incidence is in the sixth decade It is extremely rare in the young Kimmelstiel and Porter found only 3 cases before the age of twenty The large majority occur in mild diabetics often as mentioned above the diabetes is discovered only after other manifestations of glomerulosclerosis have developed There is considerable correlation between the duration of diabetes and the incidence of glomerulosclerosis Henderson *et al* found that in their cases with nodular renal lesions the average known duration of diabetes was 11 2 years That diabetic glomerulosclerosis may develop in less than four years is shown by Derow and Schlesinger's[9] observation of advanced lesions in a diabetic of 8 years duration in whom nephrectomy four years before death for suspected neoplasm had shown no changes

PATHOLOGICAL ANATOMY

The kidneys may be of normal size or somewhat enlarged Diabetic glomerulosclerosis *per se* apparently does not lead to contracted kidneys The gross appearance notably the presence or absence of granulation is largely determined by associated arterio or arteriolosclerosis In the exceptional cases in which the hypertension has entered the malignant phase with arteriolar necrosis there may be hemorrhages The deposition of lipid is often evident in the cut section

The characteristic histologic alterations are in the *glomeruli*. They consist in hyaline acidophilic deposits of spherical or oval shape. The nodules are generally in the center of a lobule. The spherules vary from 20 to over 120 microns in diameter. The nodules usually appear quite homogeneous but Allen states that higher magnification and silver staining reveal them to be circumferentially laminated. Surrounding the hyaline mass are sometimes circumferential layers of flattened cells and there may be a rim of dilated capillaries. Nodules may be present in only a small proportion of the Malpighian corpuscles and found only after search or they may be numerous, involving almost all the glomeruli with multiple hyaline masses of varying size in individual tufts. The hyaline bodies give the appearance of being located between the capillaries of the tuft, for

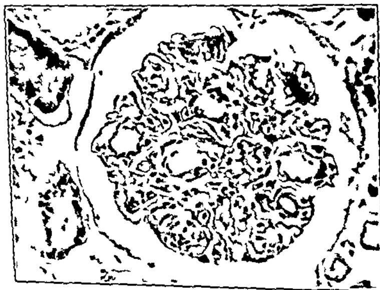


Fig. 1. Characteristic nodular lesions of diabetic glomerulosclerosis in a diabetic of many years standing who succumbed to ascending cholangitis (N P N 60 mg per cent ten days before death)

which reason Kimmelstiel and Wilson originally coined the term intercapillary glomerulosclerosis. More recent histological observations by Allen and Bell indicate that the hyaline masses originate in localized thickening of the capillary wall; according to Bell there is thickening, splitting and fusion of the inner capillary basement membranes. Using the periodic acid Schiff staining technique which sharply delimits the basement membrane, Rinehart[31] *et al.* likewise find that the lesion is initiated as a thickening of the endothelial component of the basement membrane.

The nodules just described are not the only alterations in the Malpighian tufts of diabetics. More common is a widespread nonnodular hyalinization of similar staining characteristics. Bell has termed this the *diffuse* type of

diabetic glomerular lesion. The diffuse changes are always to be found when the nodular lesions are present, but often occur in the absence of the latter. The diffuse and nodular lesions are doubtless morphologic variants of the same process, the nodular lesions represent an advanced stage.

The nature of the hyaline deposit in the nodules and diffuse lesions is not known. In appearance they closely simulate amyloid, but specific amyloid stains are negative. Lipid stains also are negative apart from occasional minute droplets scattered in the large hyaline mass. Presumably the hyaline is largely protein but Allen found it highly resistant to tryptic digestion. With the Mallory-Heidenhain stain Allen observed that the hyaline nodules generally take the deep blue of collagen but that incompletely collagenized foci stain pink or purple orange. The hyaline stains pale yellow with Van Gieson.



Fig 18 — Another section from the same kidney as Figure 17 showing the marked arteriolosclerosis

The nodular lesions are almost histologically diagnostic of diabetes. It is true that in very rare instances similar appearances are seen in chronic glomerulonephritis or the arteriolosclerotic kidney of essential hypertension. But these are so exceptional that a histological diagnosis of diabetes can be ventured with a high degree of confidence when the typical glomerular nodules are seen. Nodular lesions in glomerulonephritis are accompanied by diffuse changes in the glomeruli which reveal their nature. In the rare instances in which typical isolated nodular lesions are seen without a clinical history of diabetes the possibility exists that sugar tolerance tests would have revealed the disturbance of carbohydrate metabolism; it is just the mild forms of diabetes that furnish the main contingent of the Kimmelstiel-Wilson syndrome. While the diffuse hyalinization described

by Bell is even more common than the nodular form in diabetics it does not *per se* enable the histologic diagnosis of diabetes

The glomerular hyalinization together with the arteriolar sclerosis to be described in the next paragraph terminate in obliteration of varying numbers of the glomeruli with atrophy of the appertaining tubules

In kidneys the seat of the glomerular lesions just described there is almost invariably marked hyaline thickening of the afferent *arterioles* The efferent arterioles also often exhibit pronounced hyalinization Though the thickening of the efferent vessels is not as great as that of the afferent it is often of a degree hardly observed in any other condition detection of

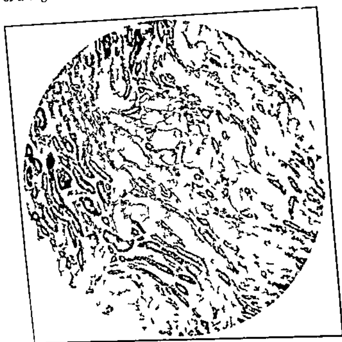


FIG 19 —Armanni Ebstein cells in the tubules of the kidney in diabetes mellitus The bodies of the cells which were filled with glycogen during life are practically unstained so that the cell border is very sharp

marked hyalinization of the vasa efferentia should awaken the suspicion of diabetes While arteriolar sclerosis is almost always found in diabetic glomerulosclerosis it is not the cause of the latter For one thing there are rare instances of diabetic glomerular lesions without notable arteriolar sclerosis this was true in a sixteen year-old girl with severe diabetes of ten years duration studied by Laipply *et al* And one often sees spherical lesions in an individual glomerulus with little hyalinization of the appertaining arterioles Thickening and elastosis of the interlobular arterioles are common

The *tubules* often exhibit considerable changes though these are not specific There is usually cloudy swelling and deposition of lipid in the

basal portion of the epithelial cells, most marked in the proximal convoluted tubules. Both isotropic lipids and cholesterol esters may be found. The deposition of lipid in the tubular epithelia is probably a storage phenomenon resulting from reabsorption of lipids from the glomerular filtrate, into which they penetrate as a result of increased permeability of the diseased glomerular loops to the frequently lipemic plasma. Casts and desquamated epithelia are often seen in the tubular lumens. There may be foci of tubular atrophy with replacement fibrosis; in these areas lipids are often demonstrable.

Glycogen Vacuolization.—In the pre-insulin days it was common to find in the kidneys of diabetics dying in acidotic coma extensive deposition of glycogen in certain parts of the urinary tubule. This deposition produces the large clear cells known as Armanni-Ebstein cells, in which the cytoplasm appears almost unstained in the hematoxylin-eosin preparation and stains red with Best's carmine. The deposition of glycogen is generally described as occurring in Henle's loop, but Baehr[10] showed that the cells involved are those of that portion of the tubule which connects the proximal convoluted tubule with Henle's loop. Glycogen may also be present in the epithelial cells and lumen of Bowman's capsule. The appearance of glycogen is not to be regarded as a degenerative change but rather as a phenomenon of storage in some way connected with the hyperglycemia and glycosuria. The glycogen is presumably polymerized from glucose reabsorbed from the glomerular filtrate (*cf.* Oliver[11]). There is no evidence that the storage of glycogen in the renal cells produces clinical manifestations. Since the introduction of insulin, Armanni-Ebstein cells are very rarely seen.

Atherosclerosis of great severity is common in the renal artery and its large and small branches in diabetic glomerulosclerosis. Hall[9] observed it in all of 8 cases of the Kimmelstiel-Wilson syndrome which succumbed to uremia and believes that it played an important part in the widespread glomerular obliteration present in these cases.

NATURE OF DIABETIC GLOMERULOSCLEROSIS

Since the cause of diabetes is unknown and its basic nature obscure—the widely held theory of primary disease of the islets of Langerhans has great weakness (*cf.* Mirsky[12])—it is not surprising that even less is known of the pathogenesis of glomerulosclerosis. However, several correlations seem relevant.

1. The development of glomerulosclerosis is correlated with the duration of the diabetes and not with the severity of the disturbance in carbohydrate metabolism as measured by the amount of insulin needed for control.

2. With only the rarest exceptions, intercapillary glomerulosclerosis is associated with arteriolar sclerosis in the kidneys.

3. In every necropsy that reveals intercapillary glomerulosclerosis widespread arteriosclerosis is found of a severity far beyond that corresponding to the age. This is the more striking the younger the patient.

4. If diabetics live long enough, a very high proportion develop glomerulosclerosis and the percentage rises asymptotically the longer the duration

of the disease This is well brought out by the studies of Dolger[13] In 200 diabetics whom he followed for up to twenty five years, not one escaped retinal hemorrhage and 50 per cent of the patients who developed retinopathy exhibited proteinuria and hypertension at the time of the earliest retinal hemorrhage

5 It does not appear to be proved that control of the disturbance in carbohydrate metabolism by diet and insulin lessens the incidence or postpones the onset of glomerulosclerosis And in patients who already have evidences of glomerulosclerosis the writer has seen no evidence that as good dietary and insulin control of the abnormality in carbohydrate metabolism as is feasible retards the progression of the renal disease

6 In a dog which Lukens and Dohan[14] kept diabetic for five years by injections of pituitary extract they observed hyaline lesions in the glomeruli which they regarded as analogous to intercapillary glomerulosclerosis

These observations are consistent with the conception that intercapillary glomerulosclerosis—like the disturbance in carbohydrate metabolism the arteriosclerosis and arteriolosclerosis and the retinopathy—is an intrinsic component of diabetes It usually first becomes manifest long after the decreased sugar tolerance but ultimately reaches a demonstrable stage in the vast majority of cases of sufficiently long duration Glomerulosclerosis appears to be the analogue in the glomerular capillaries of the arteriosclerosis artiolosclerosis and retinal capillary aneurysms and phlebosclerosis (p 512) in other categories of vessels which likewise ultimately afflict practically all long standing diabetics these changes often parallel one another and presumably have pathogenetic factors in common Contemporary thinking generally has assumed that these widespread vascular lesions in diabetes are consequences of a primary disturbance in carbohydrate metabolism but this is not proved (cf Mirsky and Dolger)

CLINICAL PICTURE

Diabetic glomerulosclerosis presents itself under many guises Manifestations correlated with diabetes—the glomerulosclerosis arteriosclerotic disease in the heart extremities brain or other organs and diabetic retinopathy and neuropathy—are variously commingled any may predominate Most often the symptoms of glomerulosclerosis appear in an individual known to have had diabetes usually mild for years less commonly glomerulosclerosis leads to discovery of previously unknown diabetes Remarkably enough diabetes often becomes milder as the Kimmelstiel Wilson syndrome evolves with a lessening in insulin requirement and patients with the full blown clinical picture of diabetic glomerulosclerosis rarely go into acidotic coma (cf Zubrod et al[15])

The most common initial indication of glomerulosclerosis is proteinuria in a diabetic with hitherto negative urine and without other evidences of heart failure In other instances manifestations of coronary or other arteriosclerotic disease hypertension impairment of vision nephrotic edema symptoms of diabetic neuropathy or rarely uremia may inspire the investigations that uncover renal disease

basal portion of the epithelial cells, most marked in the proximal convoluted tubules Both isotropic lipids and cholesterol esters may be found The deposition of lipid in the tubular epithelia is probably a storage phenomenon resulting from reabsorption of lipids from the glomerular filtrate, into which they penetrate as a result of increased permeability of the diseased glomerular loops to the frequently lipemic plasma Casts and desquamated epithelia are often seen in the tubular lumens There may be foci of tubular atrophy with replacement fibrosis in these areas lipids are often demonstrable

Glycogen Vacuolization —In the pre-insulin days it was common to find in the kidneys of diabetics dying in acidotic coma extensive deposition of glycogen in certain parts of the urinary tubule This deposition produces the large clear cells known as Armanni Ebstein cells in which the cytoplasm appears almost unstained in the hematoxylin-eosin preparation and stains red with Best s carmine The deposition of glycogen is generally described as occurring in Henle's loop but Baehr[10] showed that the cells involved are those of that portion of the tubule which connects the proximal convoluted tubule with Henle s loop Glycogen may also be present in the epithelial cells and lumen of Bowman s capsule The appearance of glycogen is not to be regarded as a degenerative change but rather as a phenomenon of storage in some way connected with the hyperglycemia and glycosuria The glycogen is presumably polymerized from glucose reabsorbed from the glomerular filtrate (*cf* Oliver[11]) There is no evidence that the storage of glycogen in the renal cells produces clinical manifestations Since the introduction of insulin Armanni Ebstein cells are very rarely seen

Atherosclerosis of great severity is common in the renal artery and its large and small branches in diabetic glomerulosclerosis Hall[9] observed it in all of 8 cases of the Kimmelstiel Wilson syndrome which succumbed to uremia and believes that it played an important part in the widespread glomerular obliteration present in these cases

NATURE OF DIABETIC GLOMERULOSCLEROSIS

Since the cause of diabetes is unknown and its basic nature obscure—the widely held theory of primary disease of the islets of Langerhans has great weakness (*cf* Mirsky[12])—it is not surprising that even less is known of the pathogenesis of glomerulosclerosis However several correlations seem relevant

1 The development of glomerulosclerosis is correlated with the duration of the diabetes and not with the severity of the disturbance in carbohydrate metabolism as measured by the amount of insulin needed for control

2 With only the rarest exceptions intercapillary glomerulosclerosis is associated with arteriolar sclerosis in the kidneys

3 In every necropsy that reveals intercapillary glomerulosclerosis widespread arteriosclerosis is found of a severity far beyond that corresponding to the age This is the more striking the younger the patient

4 If diabetics live long enough a very high proportion develop glomerulosclerosis and the percentage rises asymptotically the longer the duration

tributes In 6 patients with diabetic glomerulosclerosis Corcoran Taylor and Page[17] found the nature of the impairment of renal function similar to that in glomerulonephritis glomerular filtration and renal blood flow were diminished with an elevated filtration fraction and tubular excretory capacity was diminished Hogeman[18] likewise observed decreased blood flow and filtration but found a diminished filtration fraction Studies of renal blood flow glomerular filtration and tubular function in the Kimmelstiel Wilson syndrome by Robertson[19] *et al* revealed no characteristic differences from chronic glomerulonephritis this would be anticipated from the anatomical findings

With azotemia *anemia* usually develops It is of the same character as the anemia found in other forms of renal insufficiency

Edema —In exceptional instances swelling of the feet is the first indication that glomerulosclerosis is developing Most often however, edema is a late manifestation if it appears at all The edema may be either nephrotic or cardiac in origin perhaps most often both hypoproteinemia and heart failure enter into its causation *There* may be a classical nephrotic syndrome with anasarca massive proteinuria hypalbuminemia inversion of the albumin/globulin ration and hypercholesterolemia That the hypercholesterolemia in such cases is actually part of a nephrotic syndrome and not directly due to the diabetes is shown by its persistence despite a normal blood sugar level and absence of ketosis as a result of insulin control Following diabetic patients over many years Mann[9] *et al* found that coincident with the development of clinical manifestations of glomerulosclerosis the serum cholesterol rose above normal in 19 of 20 instances As in other forms of the nephrotic syndrome Mann observed that the rise in cholesterol correlated well with the fall in serum albumin

Arteriosclerotic Complications —Almost every patient with diabetic glomerulosclerosis sooner or later has symptoms due to arteriosclerosis Most common and important is coronary disease which often leads to heart failure and/or angina pectoris Coronary thrombosis is an ever present danger and terminates some of the cases There may be symptoms due to arteriosclerosis of the lower extremities or brain In a high proportion of patients with diabetic glomerulosclerosis the clinical picture is dominated by coronary or other arteriosclerotic complications

Diabetic Retinopathy —Most though not all patients with glomerulosclerosis sooner or later exhibit retinal lesions They may be of three varieties (apart from the now almost extinct lipemia retinalis)

1 Hypertensive retinopathy (p 368)
2 Arteriosclerotic retinopathy (p 382)
3 Specific diabetic retinopathy This process is part and parcel of the diabetes itself and often so characteristic as to enable the ophthalmoscopic recognition of the disease

Of these pathogenetically diverse retinal lesions in diabetes specific diabetic retinopathy is by far the most common Combinations of two or three of the lesions are not infrequent Henderson *et al* found specific diabetic retinopathy in 86 per cent of their diabetics who showed advanced glomerulosclerosis at necropsy However it may also occur in diabetics who do not have post mortem evidence of glomerulosclerosis It is there

The Urine.—Proteinuria occurs in all the clinically recognizable cases and may long be the only sign. Often it is slight or intermittent when first detected. In most patients the proteinuria becomes more pronounced and as a rule becomes sufficiently massive to deplete the plasma albumin. The daily urine may contain more than 10 grams of protein.

The proteinuria is accompanied by hyaline and granular casts in varying number. Rifkin[16] and his collaborators have laid especial stress on the presence in the urinary sediment of doubly refractile lipids. These occur in cells, in casts or as free droplets. Rifkin *et al.* detected anisotropic lipids in the sediment in 39 of their 44 patients. They may be found only after careful search of several specimens or they may be abundant. Details regarding the detection of doubly refractile bodies will be found in the paper of Rifkin *et al.*; they state that the anisotropic particles are found chiefly in fresh acid urine. It should be remembered that cholesterol esters may be found in the sediment in all types of the nephrotic syndrome including chronic nephrosis, glomerulonephritis and amyloidosis. However, careful search by Rifkin and his associates did not reveal them in 30 patients with "hypertensive vascular disease" without diabetes. Red cells are rarely prominent in the sediment of diabetic glomerulosclerosis. Rifkin *et al.* found none in 58 per cent of their patients and only 1 to 5 per high power field in the remainder. However, I have several times seen more numerous red cells in diabetic glomerulosclerosis, and gross hematuria may occur in the rare instances in which the hypertension enters the malignant phase.

The Blood Pressure.—Hypertension is a common but not constant manifestation of diabetic glomerulosclerosis. When a diabetic develops the proteinuria which subsequent observation proves to have been the initial sign of intercapillary glomerulosclerosis, the blood pressure is often normal and may remain so for years. But sooner or later in most cases the blood pressure rises. Laipply *et al.* give the incidence of hypertension as 67 per cent, Henderson as 60 per cent and Rifkin *et al.* as 90 to 95 per cent. In the experience of the writer, if the patients are followed throughout their course and do not have a myocardial infarction, hypertension develops in almost all. It may be moderate or pronounced and rarely is so severe as to produce the clinical picture of malignant hypertension. Usually the concomitant arteriosclerotic loss of elasticity of the aorta and other large vessels leads to proportionately greater systolic than diastolic hypertension. Often there is marked systolic hypertension without definite rise in the diastolic tension. The relatively lesser elevation of the diastolic (and mean) pressure is perhaps a factor in the rarity of malignant hypertension.

Renal Function.—In most of the cases renal function sooner or later becomes impaired. This is documented by hyposthenuria and azotemia. The latter may be present when kidney disease is first suspected or appear only after years of proteinuria. The rate of progression of the renal insufficiency may be slow and the patient survive for even two or three years after azotemia is first detected. Many of the patients die in uremia. Often the terminal picture is that of combined cardiac and renal insufficiency. The renal failure is usually due to both the specific glomerular lesions and arteriolosclerotic changes, and heart failure often also con-

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Micro-Aneurysms and Hemorrhages.—The first ophthalmoscopic finding in diabetic retinopathy consists of small red dots obviously containing blood in the presence of normal arteries (*cf.*, however, under veins). The red areas are small, mostly rounded and sharply delimited; often they are punctate and vary from a few to many. They are mostly situated in the deeper layers of the retina in the vicinity of the macula. A remarkable feature is that the small red areas may persist unchanged for weeks or months at a time. Others disappear, or they may become larger, more irregular in outline and darker in color. For months the sanguineous areas may be the only ophthalmoscopic change.

The red areas just described were long all regarded as hemorrhages. However, in 1943 Ballantyne and Loewenstein[1] demonstrated that some of the red points that have been regarded as hemorrhages are actually micro-aneurysms of the retinal capillaries about 30 to 90 microns in diameter. Their preparations show globular distentions of the retinal capillaries bordered by a definite wall in which endothelial cells are sometimes demonstrable and packed with red cells. Ballantyne found them largely situated in the inner nuclear layer. He believes these miliary aneurysms to be the earliest visible manifestation of diabetic retinopathy and this has been confirmed by subsequent experience. The micro-aneurysms may rupture and produce petechial hemorrhages or perhaps be organized and thus form some of the pin point "exudates" so often seen in the diabetic fundus. By histological examination Wexler and Bronower[22] found micro-aneurysms in each of 14 and Friedenwald[23] in 57 per cent of 76 diabetic patients. They were present in every instance of the Kimmelstiel-Wilson syndrome studied by Ashton.[24] The pathogenesis of the micro-aneurysms is obscure. Ballantyne has observed swelling and fatty change in the capillary endothelium and suggests for further consideration the hypothesis that resulting weakening of the capillary wall combined with venous stasis (the veins are often dilated) may produce the aneurysmatic dilatation. Ashton showed that the micro-aneurysms arise from the venous side of the capillaries, and they have been observed in non-diabetics with retinal venous stasis. Of especial interest is Ashton's[25] demonstration of micro-aneurysms in the glomerular tufts in the Kimmelstiel-Wilson syndrome. Friedenwald[26] found that the hyaline in the glomerular nodules and in the walls of the retinal micro-aneurysms are tinctorially identical. The findings of Ashton and Friedenwald indicate strongly that the retinal and glomerular lesions are manifestations of the same process in the capillaries. Observations with the tourniquet test indicate that capillary fragility is increased in almost all patients with diabetic retinopathy (*cf.* Wagener[27]). For an excellent survey of retinal micro-aneurysms, the reader is referred to Wagener.[28]

Exudates. The initial hemorrhages of diabetic retinopathy are usually joined by exudates. Or the latter may be seen alone at the start. The exudates are characteristically hard, *i.e.*, sharply delimited, dense and of a waxy appearance. At the start they are generally minute dots which then enlarge and often coalesce. They tend to form clusters, especially in the macular region. The color is generally yellowish white and they are highly refractile. Sometimes there are also soft, cotton wool patches

fore not a result of the renal disease Diabetic retinopathy is also not due to retinal arteriosclerosis or to hypertension, for it not uncommonly occurs in the absence of either or both, Ballantyne[1] found that over 50 per cent of diabetics with retinal lesions have normal blood pressure, though in my experience hypertension is absent in less than one quarter of patients with diabetic retinopathy Nor does the incidence of retinopathy have any relation to the severity of the disturbance in carbohydrate metabolism, for it most often occurs in mild diabetics without acidosis and seems to be neither prevented nor improved by insulin control (*cf* Dolger[12]) At present little more can be said about the pathogenesis of diabetic retinopathy than that it is an intrinsic manifestation of diabetes Indeed, it

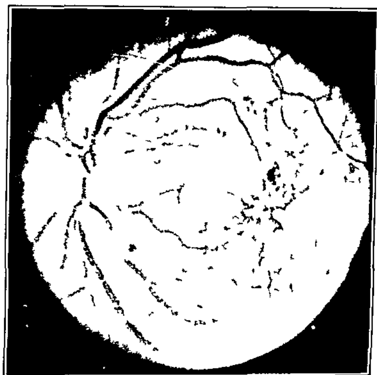


Fig 20 —Retinopathy in diabetic glomerulosclerosis (Courtesy of the late Dr Robert K Lambert)

appears to be an almost inevitable expression of the disease if the latter lasts long enough as mentioned above Dolger observed retinal hemorrhages (probably largely micro aneurysms) in every one of 200 diabetics followed up to twenty-five years

What is here termed diabetic retinopathy was long ago described by Hirschberg [2] as pathognomonic of diabetes under the designation central punctate retinitis The ophthalmoscopic picture is compounded of micro aneurysms, hemorrhages exudates and changes in the veins The arteries appear normal unless there is complication by hypertensive or arteriosclerotic retinopathy Papilledema is not part of the picture of diabetic retinopathy when present, it results from hypertension

coworkers 32 died of disease of the cardiovascular apparatus (14 congestive failure 10 gangrene 5 cerebral vascular accidents 2 myocardial infarction, 1 cardiac dilatation) and only 1 of renal insufficiency In my experience a much higher proportion of deaths has been due to renal insufficiency (5 of 15 consecutive cases) than in Henderson s series However the patients may get along for two or even three years after developing azotemia Often cardiac and renal failures are commingled Nowadays it is a great rarity for patients with glomerulosclerosis to succumb to acidotic coma unconsciousness due to a cerebral vascular accident is much more common A tragic feature is the high incidence of severe impairment of vision Of Dolger s 200 diabetics followed up to twenty five years 27 became partially or totally blind

TREATMENT

The treatment of diabetic glomerulosclerosis is purely symptomatic No available measure results in regression of the glomerular lesions or even retards their progress While the disturbance in carbohydrate metabolism should be adequately controlled by diet and insulin as in all diabetics it has not been proved that such control retards the progress of the glomerulosclerosis As with arteriosclerosis there are differences of opinion whether or not a well controlled diabetic is less apt to develop glomerulosclerosis than one who is not as careful and goes through repeated acidotic episodes Brief data from the Joslin Clinic indicating that good control militates against the development of arteriosclerosis and glomerulosclerosis have been published by Mann[20] *et al* Detailed statistics from the same Clinic collated by Wilson *et al*[30] indicate that even after twenty to thirty four years of diabetes patients who have had what they regard as good or excellent control very rarely develop diabetic retinopathy or nephropathy Likewise O Brien and Allen[6] mention briefly that diabetic retinopathy may recede under good control Contrariwise Tolstoi[27] and Dolger[11] have not found this to be the case My observations do not establish that rigid control of the abnormality in carbohydrate metabolism tends to prevent or ameliorate glomerulosclerosis Many patients who tend to their diabetes with religious fervor develop arterial and renal manifestations And the fact that in some patients with glomerulosclerosis the disturbance in the carbohydrate economy is so mild that it can be demonstrated only by a glucose tolerance test hardly indicates that meticulous control will avert the glomerular changes For these reasons I do not believe it wise to circumscribe the mild diabetic s life too narrowly and subject him to episodes of hypoglycemia in the hope of averting arteriosclerosis and glomerulo clerosis

In the vascular manifestations of diabetes as in arteriosclerosis in non diabetics cholesterol restriction and the administration of such lipotropic substances as choline methionine and inositol have been widely used However Keys has shown that cholesterol restriction lowers the cholesterol content of the plasma only if the *total lipid* content of the diet is reduced to extremely low amounts for example by a rigid rice fruit diet Keys[24] findings indicate that to lower the plasma cholesterol level the cholesterol content of the diet must be less than 200 mg daily and even vegetable

these generally bespeak coincident hypertensive retinopathy, but Wagener finds that they may also result from such complications as pregnancy, carbuncle or gangrene Wagener states that the ophthalmoscopically observed white plaques have been shown to consist exclusively of an albumin rich extravasation into the internuclear layer of the retina with essentially no fibrin masses or cellular elements Only an occasional fat granular cell is found " Most of these patients have a high beta globulin content of the plasma and the deposit may well contain giant lipoglobulin molecules

The Veins —Nettleship[4] long ago observed dilatation and beading of the retinal veins in diabetes But only in recent years has there been adequate appreciation of the importance in diabetic retinopathy of changes in the retinal veins and the lesions in the retina and vitreous resulting from the latter Ballantyne found the retinal veins enlarged and tortuous in about one third of diabetics and quotes Loewenstein's observation that such dilatation was present in 6 of 15 diabetic children without other ophthalmoscopic changes Usually later in the course of diabetic retinopathy, the changes in the veins may become severe and have drastic consequences for the eye The veins may become dilated beaded and tortuous to such a degree that they have a corkscrew-like course or form loops and varicosities Networks of what seem to be newly formed veins may appear These may extend into the vitreous Histologically, marked phlebosclerosis is found Venous bleeding leads to large hemorrhages into the retina and/or the vitreous retinitis proliferans retinal detachment and secondary glaucoma are among the complications of the late stages The resulting loss of vision is perhaps the greatest of the tragedies of diabetes and seems to be steadily becoming more common as diabetics live longer (for discussions of the venous changes *cf* O Brien and Allen[5] Ballantyne and Wagener)

As indicated above, diabetic retinopathy may be complicated by changes due to hypertension or to retinal arteriosclerosis These hypertensive and arteriosclerotic changes do not differ from those found in nondiabetics and have been described in Chapter 12 The hypertension rarely enters the malignant phase with papilledema

Arteriosclerotic and Neuropathic Complications —These are even more common in individuals with glomerulosclerosis than in the general run of diabetics Arteriosclerotic heart disease is the most common cause of death Arteriosclerotic complications in the extremities and brain are also frequent Cord bladder and other manifestations of diabetic neuropathy are not rare

PROGNOSIS

The prognosis of diabetic glomerulosclerosis is poor Most often the course is downhill albeit intermittently and not rarely at a slow pace The average duration of life after the appearance of proteinuria retinopathy or another initial manifestation is probably about three years However some patients get along for six years or even more Of 22 cases of glomerulosclerosis studied by Rifkin *et al* at necropsy 9 succumbed to uremia 7 to heart failure 2 to acute coronary occlusion and the others to unrelated causes Of the 61 necropsy observations of Henderson[7] and his

Chapter

18

THE AMYLOID KIDNEY

AMYLOIDOSIS of the kidneys is primarily an affection of the glomeruli. While amyloid is often deposited in the walls of the arteries and arterioles as well as in the basement membrane of the tubules, the clinical manifestations largely result from the lardaceous transformation of the glomerular loops. The tubular changes seem to be largely secondary to the glomerular amyloidosis as a result of interference with their blood supply and athrocytosis of protein and lipid from the glomerular filtrate. The most common clinical manifestation is proteinuria, which may be massive enough to entail hypoproteinemia and a *nephrotic syndrome*. The secondary implication of the tubules may also result in hyposthenuria and polyuria. Exceptionally, the glomerular disease is extensive enough to produce renal insufficiency with uremia and hypertension—the amyloid contracted kidney. From the morphological point of view the amyloid kidney is a nephrosis, for the lesions are degenerative, and Volhard and Fahr[1] designated it as amyloid nephrosis. Both the clinical and anatomical pictures of renal amyloidosis resemble somewhat those of diabetic glomerulosclerosis. Pathogenetically, also, these two conditions may be allied in that both represent changes in the glomerular capillaries resulting from alterations in the chemical composition of the plasma.

The amyloid kidney was first described by Rokitansky,[2] who named it "bacon kidney" (Speckniere); the analogous expression lardaceous kidney is still used by the English. The characteristic reactions with iodine and sulphuric acid were described by Meckel,[3] who thought amyloid to be cholesterol. Because of the iodine reaction Virchow[4] considered the substance to be related to cellulose and therefore coined the word amyloid. The term amyloid has persisted though it is known since the researches of Friedreich and Kekule[5] that the substance in question is not a carbohydrate but a protein. The clinical features of amyloid disease of the kidneys were described by Wilks,[6] Todd[7] and Traube.[8]

OCCURRENCE OF RENAL AMYLOIDOSIS

Three etiological categories of amyloidosis may be differentiated:

1. *Primary amyloidosis*, in which the lardaceous deposits develop in the absence of known cause. Long ago described by Litten,[9] such cases are rare; in 1946 Eisen[10] found only 46 in the literature and added 2. In many of these cases the amyloid does not stain classically with Lugol's solution, Congo red and methyl violet (para-amyloid). The distribution of

fats must be excluded This entails a very rigorous regime, and its value in the treatment of arteriosclerosis and glomerulosclerosis is still decidedly *sub judice* As has been said, one should beware of merely making the patient's life seem longer without actually prolonging it

The treatment of edema, renal insufficiency and the other manifestations of glomerulosclerosis is purely symptomatic and does not differ from that in nondiabetics, the reader is referred to the relevant chapters Coronary insufficiency, myocardial infarction and congestive heart failure are treated as in nondiabetics Perhaps the saddest chapter in the treatment of diabetes is our inability to help diabetic retinopathy Since the process is characterized by hemorrhages in the early stages, and because increased capillary fragility has been found, rutin and ascorbic acid have been used In the writer's experience they have been worthless

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Because of the important role of tuberculosis in the causation of amyloid disease it is most often found in young adults This is illustrated in the following table given by Dickinson[17]

Age	Number of cases
0 to 10	3
11 to 20	11
21 to 30	21
31 to 40	10
41 to 50	10
51 to 60	3
61 to 70	3
Over 70	0

Of these 61 cases 36 were in males and 25 in females

Amyloid disease of the kidneys of any considerable extent is almost always accompanied by similar deposits in the liver and spleen The adrenals intestine and lymph glands are also often involved and lardaceous change may more rarely be found in almost any other organ Apart from generalized amyloidosis due to a systemic cause localized amyloid deposits occur on rare occasions particularly in connection with cartilage as in the trachea and larynx

NATURE OF RENAL AMYLOIDOSIS

Amyloid is not deposited in the cells but always between the tissue elements In all organs it shows a predilection for the vessel walls being deposited around the capillaries or in the walls of the small arteries and veins between the medial muscle cells or under the endothelium

The chemical nature of amyloid is not well known It contains nitrogen yields amino acids on acid hydrolysis and is split by proteolytic ferments though with difficulty It is therefore undoubtedly a protein Krawkow found that amyloid consists of a protein conjugated to chondroitin-sulphuric acid a substance present in cartilage But Hannsen[18] did not find chondroitin sulphuric acid in amyloid isolated from the spleen It is probable that amyloid in different organs and at various stages of aging differs in composition this is indicated by the results of analyses and by variations in the staining reactions

The most important color reaction of amyloid is with iodine Lugol s solution stains it a mahogany or walnut brown This is sharper after preliminary treatment with acetic acid Subsequent addition of dilute sulphuric acid may change this to a blue or green tint With methyl violet and some other dyes amyloid stains metachromatically a red color resulting The great affinity of amyloid for Congo red is the basis of a diagnostic test (p 525) These reactions are not invariable I once saw severe generalized amyloidosis in a syphilitic patient which stained with neither iodine nor methyl violet Macallum[19] mentions a similar case The staining reactions apparently vary with the age of the amyloid The classical staining reactions are especially apt to be absent in primary amyloidosis and amyloidosis secondary to myelomatosis These findings indicate that amyloid varies in chemical composition

the amyloid is also apt to be atypical (as compared to the common secondary amyloidosis) with great tendency to deposits in the heart, tongue and gastro-intestinal tract Congestive heart failure, macroglossia and skin lesions are present in considerable proportions of the cases (*cf* Eisen)

2 *Amyloidosis complicating multiple myeloma* This occurs in about 5 to 10 per cent of patients with myelomatosis In these cases the amyloid is apt to have atypical distribution The distribution and staining reactions are akin to those in primary amyloidosis

3 *Secondary amyloidosis*, which results from chronic suppuration or certain other processes in which there is great tissue destruction This is the common variety of amyloidosis the incidence of the other two types is trivial in comparison

According to the figures collated by Eisen the kidney is involved in 26 per cent of cases of primary amyloid, 29 per cent of amyloid complicating multiple myeloma and 72 per cent of secondary amyloidosis Dahlin[11] found the kidney infiltrated in 93 per cent of his cases of secondary amyloidosis

Secondary amyloidosis occurs almost exclusively in the chronic cachexias, more particularly those characterized by long-standing suppuration The most common cause is tuberculosis (41 of Saleeby s[1] 50 cases) especially in the presence of pulmonary cavities or bone or joint sinuses Amyloidosis is more apt to complicate tuberculosis in an inactive afebrile stage than when it is progressive and accompanied by high fever Another common cause in pre penicillin days was chronic pyogenic infection with long standing suppuration, as in empyema osteomyelitis, pulmonary abscess bronchiectasis pyonephrosis etc Extreme amyloidosis occurred in an instance of long standing purulent paranasal sinusitis While amyloidosis due to syphilis is perhaps most often found when there are old bone sinuses yet it may occur both in the congenital and acquired forms in the absence of suppuration In Hodgkin s disease malaria, leukemia gout rheumatoid arthritis and many other conditions amyloidosis has been described without any suppuration Breaking-down neoplasms are a rare cause of amyloidosis Moschcowitz[27] observed amyloidosis in ulcerative colitis a condition in which I have also once seen it Oppenheimer and Silver[13] described amyloidosis complicating arteritis and multiple gangrene of the skin the amyloid receded when the gangrene cleared up I saw one instance of extreme generalized amyloidosis accompanying subacute bacterial endocarditis in which it is apparently very rare Beatty[14] observed 4 cases in which amyloidosis was associated with rheumatic heart disease I have not seen this association Since the introduction of the antibiotics the other improvements in the treatment of tuberculosis and the virtual disappearance of tertiary syphilis secondary amyloidosis formerly so common has decreased enormously in incidence

While amyloidosis is usually found as a result of a long standing suppuration or other process yet it can be produced very rapidly Krawkow[15] found amyloid after eleven days of experimentally produced suppuration in the rabbit Dickinson[16] saw lardaceous disease three weeks after a compound fracture and other observations of even shorter periods have been reported

smooth pale often glassy, butter yellow or ochre surface the French compare the color to that of old ivory Much less commonly, the kidney is reddish brown (red amyloid kidney) The consistency is increased and the kidney is inelastic or even somewhat rigid If there has been very extensive fatty change the organ may be much whiter and softer, closely resembling the large white kidney of glomerulonephritis

On section it is seen that the cortex is broadened and its markings indistinct but it is sharply delimited from the medulla which is of a darker brown color The kidney substance appears rather translucent and may be greasy if much fat is present The glomeruli can usually be made out



Fig 21 —Amyloid contracted kidney complicating long standing chronic pneumonitis

as grayish translucent dots which may be slightly elevated Application of Lugol s solution after preliminary treatment with dilute acetic acid produces a brownish stain in which the glomeruli can be seen as dark brown points Dark brown striæ representing the straight arteries in a state of amyloid degeneration radiate from the medulla Subsequent addition of dilute sulphuric acid may change the color to dirty green or blue but this reaction is very inconstant It was mentioned above that even the iodine reaction may be absent despite extensive amyloidosis Thrombi are some times present in the small veins

In the later stages atrophy of the parenchyma and replacement fibrosis result in the *amyloid contracted kidney* The kidney becomes smaller and

Amyloidosis can be produced in mice and other animals by causing long-standing suppuration or by the repeated injection of toxins. This was first done by Birch Hirschfeld[20] in 1882, who produced suppuration in a rabbit by the inoculation of pus from a patient with caries and observed the development of amyloid in the spleen within six weeks. Since then, amyloid has been produced with pure cultures of staphylococci, Bacillus pyocyaneus and various other organisms, as well as with pyocyaneus and other toxins. Horses used to make diphtheria antitoxin often have amyloid. Frank[21] produced amyloidosis in white mice by the injection of a bacillus of the Friedlaender group, but his conclusion that amyloidosis is always due to such infection is unsupported.

A new line of investigation was opened by the experiments of Kuczynski,[22] who produced amyloidosis in white mice by feeding them with eggs, milk and cheese. He found that while the first degradation products of casein also produce amyloid, peptones do not. From these experiments, Kuczynski concluded that an essential factor in the production of amyloidosis is the circulation of protein complexes that undergo further degradation. In good accord with this view is the fact that amyloid is itself a protein and that it almost always appears in the presence of marked tissue destruction. Letterer[3] and others have brought forward considerable evidence that at least often the proteins in question are globulins and that hyperglobulinemia is often concerned in the genesis of amyloidosis. This view is strongly supported by the experiments of Eklund and Reimann,[24] who found hyperglobulinemia in rabbits in which amyloidosis was produced by repeated injections of sodium caseinate. Also concordant are the observations of Hoffman[5] *et al.* who found that protracted feeding of large amounts of cholesterol to rabbits produces hyperglobulinemia and in some of the animals amyloidosis. The occurrence of amyloidosis in chronic suppurations, multiple myeloma and antitoxin horses of course harmonizes very well with the theory of the role of hyperglobulinemia in the production of amyloidosis. Dick and Leiter[6] and Sussman and Fried[7] have produced protracted hyperglobulinemia in rabbits by the intravenous injection of rabbit globulin. Some of Dick and Leiter's animals developed amyloid but others did not. It thus seems that either other factors in addition to hyperglobulinemia participate in the deposition of amyloid or that the latter results from the circulation of only certain, as yet undefined, globulins.

PATHOLOGICAL ANATOMY OF RENAL AMYLOIDOSIS

Small deposits of amyloid may be present in the kidney without any change in the gross appearance of the organ. They may be brought out by the iodine test or discovered only in the sections.

The typical amyloid kidney is enlarged and heavy. While the increase in weight is usually but moderate it may be very marked; thus the amyloid kidneys of a girl, aged fourteen years, with tuberculosis of the hip of many years' duration weighed together 800 grams. The amyloid kidney is generally heavy for its size. There are unusual amyloid kidneys which are smaller than normal. The capsule strips readily, revealing a

retained while the rest of the tuft is completely replaced by amyloid a point to which Fahr[9] has called attention There is striking little reaction to the presence of the amyloid though occasionally slight proliferation of the cells of the tuft or capsule is seen Bell found that there is usually a definite increase in the endothelial nuclei of the glomeruli preceding the deposit of amyloid which he attributes to the underlying infection If the process lasts long enough the final result is complete fibrosis of the glomerulus connective tissue growing in from the capsule The next most common seat of amyloid deposition is in the vasa afferentia, the larger arteries are not involved as regularly or as early The efferent arterioles may be involved in advanced cases but not as much as the afferent There are rare cases in which the arteries in the medulla alone are involved The amyloid may be deposited between the cells of the media or under the endothelium the cellular elements of the vessel wall gradually undergo atrophy from compression so that the vessel in cross-section appears like a homogeneous tube. However Oliver's[30] dissections show that the distribution of the amyloid along the arteries is always patchy Another less common site of amyloid change is in the basement membrane of the tubules particularly in the medulla Rare instances have been described in which the amyloid was confined to the basement membrane of the collecting tubules particularly in the papillae Saleeby[12] found involvement of the basement membrane of the tubules in 28 per cent of his cases

In those instances in which there is but slight amyloid deposit in the glomeruli the tubules may be practically normal But in the large majority of instances alterations of greater or less extent are found in the tubular epithelium These are usually most marked in the proximal convoluted tubules and consist in fatty and lipoidal change appearance of hyaline droplets in the cell bodies and more rarely vacuolar degeneration The cells generally contain considerable amounts of fat and often also anisotropic lipoid though this does not reach the extreme degree seen in other forms of renal disease The tubules usually contain casts often in tremendous numbers The number of casts seen in the sections often seems disproportionately great when compared to the mostly moderate cylindruria during life The explanation of this discrepancy may be afforded by Oliver's finding on microdissection that some of the structures in the tubular lumens simulating casts in the sections are albuminous urine coagulated by the histological fixative and not intra vitam casts This is probably true of most of the structures in the proximal parts of the nephron Some of the actual casts in the lower nephron plug the lumen with upstream dilatation and doubtless ultimate atrophy Saleeby[12] found that the casts do not give the amyloid staining reactions However on rare occasions the amyloid basement membrane may fuse with the epithelial cells and the cast-off mass give the amyloid staining reactions (Senator[31]) It may have been such masses that were described and figured by Dickinson[32] and other older authors as amyloid casts in the renal tubules Recently Iverson and Morris[33] have demonstrated tinctorially the presence of amyloid casts in the rare primary amyloidosis

In older cases extensive atrophic changes in the tubules take place At first these consist in atrophy and collapse of individual tubules with

harder, the capsule adherent and the surface irregularly granular. In some cases, despite well marked contraction, there is little irregularity of the surface. The grayish-yellow section shows narrowing of the cortex, obliteration of the markings and absence of sharp transition between the cortex and medulla. The presence of amyloid in such a kidney can sometimes be recognized only by the application of iodine or microscopically. Grossly, the kidney may be indistinguishable from that of chronic glomerulonephritis. The amyloid contracted kidney does not attain the extreme degree of shrinkage that is sometimes seen in the primary or secondary contracted kidney.

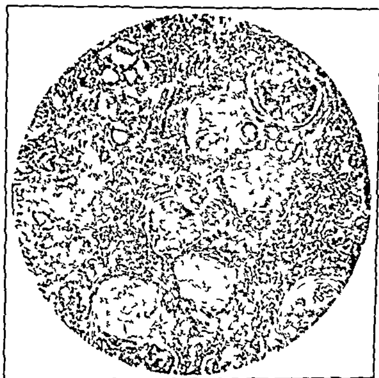


Fig 22.—Section of amyloid contracted kidney in a syphilitic. Most of the glomeruli have undergone almost complete amyloid degeneration, extensive atrophy and disappearance of the tubules with replacement fibrosis.

Microscopically it is seen that the amyloid is deposited almost entirely in the walls of the vessels, thereby accounting for the difficulty of injecting amyloid kidneys which Virchow long ago noted. The glomeruli are almost always involved and sometimes are the exclusive site of the deposition. Amyloidosis results in great enlargement of the glomeruli though they may ultimately shrink. The amyloid is laid down in the capillary loops around the endothelium. With the azocarmine stain Bell [3] has demonstrated that the amyloid is deposited on the inner surface of the basement membrane, often displacing the endothelial nuclei inwards. The final result of the process is the conversion of the tuft into an amyloid sphere in which are to be seen only remains of nuclei and sometimes not even these. But it is surprising how long the permeability of individual capillary loops may be

in the kidneys On the other hand in still other cases, renal amyloidosis does produce important symptoms There are edema and in unusual cases of amyloid contracted kidney renal insufficiency with yet more rarely arterial hypertension

The Urine —The urinary volume is variable Most commonly it is approximately normal or there may be slight polyuria of about 2000 cc daily In some instances there is marked polyuria Stewart[35] described a patient with amyloid kidney who passed 180 to 210 ounces of urine daily If edema is forming or the patient is losing water from diarrhea or vomiting there may be oliguria with deeply colored urine of high specific gravity Marked polyuria with low specific gravity is encountered in the amyloid contracted kidney as evidence of impaired renal function The onset of renal insufficiency in the unusual cases in which this occurs is marked by oliguria with low specific gravity The polyuria may be the first indication of amyloid disease

The amount of protein in the urine is often though not always very great In rare instances as much as 30 grams of protein may be lost in the urine daily (Bartels[36]) The proteinuria is very variable and at times may practically disappear Cases have been described in which well marked amyloidosis of the kidneys was not accompanied by any proteinuria whatsoever despite careful observation of the urine for a long period before death (Leube[2]) It was mentioned on page 121 that the albumin to globulin ratio in the urine in amyloid nephrosis is very low The number of casts present in the urine is usually less than in equally marked proteinuria in other forms of renal disease and they may be very scanty or absent The casts are mostly hyaline with a few granular and epithelial elements also present Often considerable numbers of waxy casts are found that the latter are not characteristic of amyloid disease was emphasized above Fatty and not uncommonly lipoidal (double refracting) casts may be found As a rule cellular elements are sparse but occasionally moderate numbers of red cells are present

The Blood —It need scarcely be mentioned that anemia is often present as a result of the primary disease If much protein is lost in the urine the total protein content of the plasma is lowered There may even be less than 4 per cent of plasma protein This has several times seemed to me to occur with less marked proteinuria than is required to lower the blood proteins correspondingly in other forms of renal disease Quite probably the usually cachectic state of the patients and perhaps amyloidosis of the liver interfere with regeneration in fact plasma protein concentrations well below the normal are not uncommon in cachectic tuberculous patients without any amyloidosis or other cause for loss of protein in the urine The albumin to globulin ratio is usually inverted in such cases sometimes markedly so Here again the basic disease is unquestionably partly at fault for a rise in globulin is common in tuberculous and other infections Sometimes the lowered protein content of the plasma is accompanied by hypercholesteremia as in other patients who lose protein in the urine I have several times seen the blood cholesterol well above 300 gm per cent and in one patient who was not cachectic it exceeded 600 mg per cent The cachectic state of most of the patients is probably the reason

small areas of replacement fibrosis In the fully developed amyloid contracted kidney, the field consists largely of cellular connective tissue in which are mostly amyloid and fibrotic glomeruli and atrophic tubules There are often also islands of greatly dilated tubules lined by low epithelium, the entire picture closely resembling that seen in other varieties of contracted kidney Only in long-standing amyloidosis among the nephroses did Oliver's studies reveal disorganization of the architecture of the kidney In such cases the vessels may show well marked endarteritis and arteriosclerotic change, but Oliver found that this occurs only in older individuals

The interrelations of the amyloid transformation of the glomeruli and the degenerative changes in the tubules are of interest It is to be remembered that amyloidosis almost always occurs in toxic states in which tubular degeneration is common even when amyloidosis is absent In their first monograph Volhard and Fahr[1] considered the amyloid change and the tubular lesions as independent consequences of the general toxic state viewing the actual amyloid change as relatively unimportant in the causation of the symptoms and as merely an unessential "complication" of the nephrosis manifested by the tubular lesions Later, Fahr[34] regarded the atrophic changes in the tubules as secondary to the glomerular amyloidosis but the hyaline-droplet change in the tubules as independent In view of the fact that almost the entire blood supply of the tubules first passes through the glomeruli, it would seem that so great an interference with the glomerular circulation as is undoubtedly caused by the amyloid change in the glomerulus must result in atrophic and degenerative processes in the appertaining tubule Moreover the degenerative changes in the kidneys of tuberculous patients without amyloidosis are at least as far as I have observed, but rarely even nearly so marked as one commonly sees with amyloidosis The view that the atrophic changes in the tubules with the formation of the amyloid contracted kidney are secondary to the glomerular changes seems to me undoubtedly correct for nephrotic contracted kidneys in the tuberculous without amyloidosis are extremely rare in rather large material I have never encountered one Moreover lipid and hyaline droplets in the tubular epithelia may well be due to athrocytosis of lipid and protein from a filtrate containing these substances as a result of heightened permeability of the diseased glomerulus So while the general toxemia very probably does cause some part of the tubular lesions it would seem that a far more important factor in their pathogenesis is the amyloid lesion of the glomeruli Plugging of tubules by casts also results in atrophy of some of the nephrons

CLINICAL PICTURE OF RENAL AMYLOIDOSIS

In most instances amyloid disease of the kidneys is of little clinical importance, the picture being entirely dominated by the basic illness A number of cases have been recorded in which the urine was free from pathological constituents and yet well-marked amyloid change in the kidneys was found postmortem Most often, there are urinary changes but the clinical course of the patient is not influenced by the presence of amyloid

Arterial Hypertension —Arterial hypertension and cardiac hypertrophy are exceptional consequences of the amyloid kidney Dickinson found cardiac hypertrophy in but 1 of 48 cases of lardaceous disease of the kidney Wagner[38] 10 instances of hypertrophy of the left heart in 265 cases In a patient with amyloid contracted kidney studied by Oppenheimer and the author[39] the blood pressure was 196 mm systolic and 116 mm diastolic and had been considerably higher prior to admission to the hospital I have since seen several other instances of hypertension due to amyloid contracted kidney It is of course obvious that the cachectic condition of most of these patients tends to inhibit the maintenance of hypertension and the development of cardiac hypertrophy even if the essential factors for their production are present It is perhaps for this reason that hypertension is rarest in the cases due to pulmonary tuberculosis

Hypertensive Retinopathy —Hypertensive retinopathy is extremely rare as one would expect from the rarity of hypertension Litten[40] saw it but twice in several hundred cases of amyloid disease and Dickinson[41] and Noble and Major[4] each mention an example Arteriosclerotic retinopathy was present in the patient referred to in the preceding paragraph

Diarrhea —Diarrhea may be present as an evidence of intestinal amyloidosis

DIAGNOSIS OF AMYLOID KIDNEY

If in the presence of chronic tuberculosis or a long standing suppuration the liver and spleen are enlarged smooth and hard so that we believe them to be amyloid it is extremely probable that amyloid disease of the kidneys is also present This holds true even though proteinuria is slight and there are few or no casts in the urine In the absence of demonstrable amyloidosis of the liver and spleen the diagnosis of amyloid nephrosis is much more difficult The urinary findings detailed above and edema in the absence of hypertension and nitrogen retention may of course occur in chronic nephrosis without amyloid Glomerulonephritis in a cachectic patient may have the same clinical features Nevertheless if such a nephrotic picture—marked proteinuria and edema with neither impairment of renal function nor hypertension—develops in the presence of chronic tuberculosis old syphilis or protracted suppuration it is highly probable that the renal disorder is amyloid nephrosis The differentiation of amyloid nephrosis and the cachectic edema that is so common in the terminal stages of pulmonary tuberculosis is often difficult for the latter may be accompanied by febrile proteinuria The same is true unless enlargement of the liver and spleen is present of the diagnosis of amyloid contracted kidney with renal insufficiency and perhaps hypertension from chronic glomerulonephritis in patients with chronic suppurations

The Congo Red Test —Bennhold[43] introduced a test for amyloidosis based on the great affinity of the colloidal dye Congo red for amyloid He found that if 10 cc of a 1 per cent solution of Congo red is injected intravenously less than 30 per cent of it disappears from the blood stream of normal persons within an hour On the other hand Bennhold stated that in the presence of amyloid disease from 40 to 100 per cent leaves the blood stream within an hour Bennhold also found that in chronic nephrosis

why the cholesterol of the blood is not as much elevated as in other varieties of renal disease with low plasma protein I have twice seen lactescent serum in such patients Nitrogen retention occurs in the rather unusual cases with renal insufficiency and may reach extreme degrees

Edema —Edema is a very common and sometimes outstanding symptom of amyloid nephrosis Dickinson found subcutaneous edema in 33 of 48 patients with amyloid kidney It is usually of insidious onset As a rule the lower extremities are first and most affected but the face may be puffy and in unusual instances great general anasarca develops Ascites is not uncommon having been present in 12 of Dickinson s cases This author found hydrothorax in but one of the patients There may be ascites in the absence of anasarca I have examined the subcutaneous edema fluid on a number of occasions and found that it is of the type that occurs in nephrotic edema *i e* it is very poor in protein On all occasions the protein content was under 0 5 per cent usually less than 0 2 per cent, and once there was almost no protein On two occasions I have seen lactescent ascitic fluid, and in one of these cases that came to necropsy was able to prove that this was not due to local disease of the peritoneum Both patients had hypercholesteremia and in one the serum was also lactescent The edema is, therefore, of the nephrotic type due to the diminished albumin content of the blood plasma

It should be borne in mind that in patients in the final stages of tuberculous and other cachexias edema particularly of the lower extremities, is common even in the absence of amyloid disease—so-called cachectic edema In such cases there may be low plasma proteins with inversion of the albumin to globulin ratio and low protein content of the edema fluid It therefore seems probable that an important factor in the genesis of cachectic edema is diminished colloid osmotic pressure of the plasma though in such patients cardiac weakness doubtless also plays a part In cachexias with amyloidosis the loss of protein in the urine is accordingly not the only factor which lowers the blood protein and thus leads to edema But edema is seen also in some patients with amyloid nephrosis who at the time are not at all cachectic the loss of protein in the urine being the only discernible factor in the pathogenesis of the dropsy In the rare primary amyloidosis, edema is most often part of the picture of congestive heart failure

Renal Insufficiency —Renal insufficiency with consequent nitrogen retention and uremia occurs in unusual instances of the amyloid contracted kidney It is possible that such cases are not so rare as is generally thought because of the desolate general condition of the patient, the blood chemistry is usually not adequately studied However it is often striking how extensive may be the amyloid change in the kidneys without producing renal insufficiency Almost all the glomeruli seen in the sections may be converted to amyloid and yet the patient at no time gave any evidence of uremia Thus may be explained by the fact, mentioned above that isolated capillary loops often remain permeable in an otherwise completely amyloid glomerulus The patient may remain for a long time in a state of compensated impairment of renal function, as shown by diminished ability to concentrate the urine but absence of retention in the blood

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the dye likewise leaves the blood stream more rapidly than normally, values of 40 to 60 per cent being found, but not over 60 per cent as in amyloid. Bennhold believed the rapid disappearance of the dye from the blood in amyloidosis to be due to two factors: (1) The dye is adsorbed by amyloid, as he showed experimentally; (2) lowered adsorption by plasma albumin, the concentration of which is diminished in these conditions. It seems probable that increased permeability of the kidney also plays a part in the rapid disappearance of the dye from the blood stream when there is marked proteinuria, the dye leaking into the urine.

Bennhold's findings were confirmed by Bookman and Rosenthal[44] and others, and the Congo red test has since been widely used for the detection of amyloidosis. However, shortcomings soon became evident. While Lipstein[45] found that more than 90 per cent of the Congo red was absorbed in 29 of 34 tuberculous patients with amyloidosis verified at necropsy, he also observed absorption of between 80 and 100 per cent of the dye in 4 of 91 individuals without tuberculosis. Selikoff[46] has studied the test in great detail and finds that the original criteria lead to both false negatives and positives. Up to 90 per cent absorption may be found in chronic nephrosis and in other conditions without amyloidosis. On the other hand, patients with small amounts of amyloid often have less than 90 per cent absorption. Less than 90 per cent absorption thus does not speak strongly for or against the diagnosis of amyloidosis. More than 90 per cent removal favors the diagnosis of amyloidosis, but exceptional instances of even 100 per cent absorption in the absence of amyloid have been observed. Selikoff states that he has not seen any case in which practically complete absorption of the dye occurred in 2 consecutive Congo red tests in the absence of amyloid. Unger[47] *et al.* have modified the technique of the Congo red test in several ways, including a thirty-minute end point, and find that the accuracy in testing for amyloid is improved. Severe reactions have occurred from some batches of Congo red (Selikoff and Bernstein[48]).

It was mentioned above that histologically the deposits in primary amyloidosis do not usually stain well with Congo red, and correspondingly Eisen[10] states that the Congo red test is more often negative than positive in this rare form of amyloidosis.

Biopsy.—The diagnosis of amyloidosis can often be established by aspiration biopsy of the liver or spleen (*cf.* Waldenstroem[49]). Selikoff and Robitzek[50] have introduced gingival biopsy for this purpose. In 18 patients with a clinical diagnosis of amyloidosis they obtained 14 positive biopsies, including cases with negative Congo red tests.

PROGNOSIS OF RENAL AMYLOIDOSIS

The prognosis in the vast majority of cases is that of the basic disease, which usually leads to death within a year or less. But cases are not rare in which amyloidosis due to such causes as tuberculosis of the bones or syphilis, lasts for years. One of Wagner's[38] patients had amyloidosis for fifteen years.

In those unusual cases in which the underlying cause of the amyloidosis can be arrested the amyloid disease may also stop its progress or even regress This applies particularly to syphilitic patients as well as to those with suppuration in an extremity which can be cured by antibiotics or amputated and to instances of pulmonary tuberculosis or empyema which heal spontaneously or are cured by medication or operation A number of cures thus attained have been reported (Gairdner[51] Herringham[52] Waldenstroem[49] Reinmann[53] and others) That amyloid can be completely absorbed once the cause has been removed is known from the experiments of Kuczynski[2] who produced amyloid by feeding casein to mice and saw it disappear after the feeding had been stopped In amyloidosis induced in rabbits by bacterial injections Dick and Leiter[6] observed reabsorption of amyloid after discontinuing the injections but not in the kidneys

TREATMENT OF RENAL AMYLOIDOSIS

The treatment of the patient with renal amyloidosis comprises (1) the therapy of the underlying disease (tuberculosis osteomyelitis syphilis etc) and (2) the management of such manifestations of the renal implication as hypoproteinemia edema renal insufficiency hypertension and heart failure much as in other forms of renal disease It is to be borne in mind that amyloidosis may disappear if the underlying cause is eliminated If syphilis is the basis vigorous antiluetic treatment is to be pursued Evidences of early amyloidosis in a tuberculous patient call for especially vigorous treatment with streptomycin and the newer chemotherapeutic agents and for surgical intervention in appropriate circumstances Suppurative processes complicated by amyloidosis call for especially vigorous antibiotic treatment In pre antibiotic days surgical treatment sometimes proved life-saving in patients with amyloidosis as in the following classical case reported by Gairdner[51]

A man was admitted with extensive necrosis of bone accompanied with all the symptoms of amyloid kidney amyloid liver albuminuria and every possible symptom of a constitution infected with amyloid disease He had been considered in the first instance too ill to be operated upon But nevertheless a venturesome surgeon did it He took off his leg This patient had reached the last degree of exhaustion connected with amyloid supervening upon disease of his bones The result of the operation was a perfect return of the normal state

Fortunately the once common and usually irremediable problem of amyloidosis is a vanishing one The elimination of gummatous luetic disease the decline in the incidence of tuberculosis and the control of pyogenic infections by antibiotics have almost eliminated clinically significant amyloidosis

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Chapter

19

ACUTE GLOMERULONEPHRITIS: ETIOLOGY, BACTERIOLOGY, PATHOLOGICAL ANATOMY AND PATHOGENESIS

Acute glomerulonephritis is a diffuse inflammation of the glomeruli of the kidneys. The glomerular lesions, however, are indicated by some evidence to be but one manifestation, albeit by far the most striking, of a process widespread in the capillaries, but this is *not proved*. The disease is doubtless always the result of an infection following tonsillitis, occurring in the third week of scarlet fever, or complicating other infections which will be mentioned in the next sections. *Acute glomerulonephritis is the variety of renal disease which was known during World War I as trench nephritis* and to clinicians of a previous generation as *nephritis a frigore* because exposure to cold sometimes appears as the exciting cause.

It would be more accurate to use the term *acute diffuse glomerulonephritis*, for there are also focal nephritides with predominantly glomerular localization (Chapter 23), but the briefer expression is reserved for the diffuse disease alone because it is far more important from a clinical point of view than the focal affections. In the past few years the term glomerular nephritis is being used with increasing frequency instead of glomerulonephritis.

The conception that one form of Bright's disease starts as an inflammation of the glomeruli, a glomerulonephritis, was introduced by Klebs[1] as a result of his observations on postscarlatinal renal disease and definitely established seventy-five years ago by the histological investigations of Langhans. Numerous studies during World War I showed that trench nephritis is an acute diffuse glomerulonephritis. The investigations of Loehlein[3] confirmed in this country by Bell and Hartzell[4] have demonstrated clearly that the highly variegated clinical and anatomical pictures of chronic glomerulonephritis are later stages of acute glomerulonephritis, the tubular, interstitial and vascular changes all ensuing subsequent to the stage of acute glomerulitis which forms the subject matter of this chapter.

ETIOLOGY OF ACUTE GLOMERULONEPHRITIS

Acute glomerulonephritis is a manifestation of an infection in one part or another of the body. While cold and other factors often play an important part as predisposing causes, recent investigations have shown more and more clearly that the primary and essential cause is infection. Longcope[5] and his coworkers were able to demonstrate infectious foci in

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85 per cent of their cases of acute glomerulonephritis The relation between the initial infection (sore throat, scarlet fever, etc) and the renal lesion is generally clear in children, but in adults there is a larger proportion of cases in which a history or other evidence of a preceding infection cannot be obtained In fact, in 2 of the above mentioned cases studied by Longcope, the infectious focus could not be demonstrated even at necropsy Nevertheless, these "idiopathic" cases are in all ways so nearly identical with those occurring in connection with a manifest infectious focus, that their origin in infection seems beyond cavil

In 976 cases of acute glomerulonephritis including 77 of their own, Hayman and Martin[6] found the following preceding infections

Antecedent infection	*Number of cases*
Sore throat tonsillitis	313
Upper respiratory tract	238
Otitis and sinusitis	56
Scarlet fever	62
Skin infections	40
Pneumonia	39
Rheumatic fever	17
Miscellaneous	101
Infection unknown	110

Occurrence —Infection in the lymphoid tissue of the throat preceded about 90 per cent of the unequivocal cases of acute glomerulonephritis in adults seen by the writer i e those patients who had edema hypertension or renal insufficiency so that focal nephritis could be ruled out with certainty Indeed, in my experience in New York City in recent years typical acute glomerulonephritis due to causes other than sore throat has been very exceptional When acute glomerulonephritis develops in patients with otitis mastoiditis sinusitis or bronchitis, and is attributed to the latter there is most often an antecedent streptococcic infection in the lymphoid tissue of the throat Those series of cases of acute nephritis in adults in which a high proportion are listed as due to causes other than sore throat probably include considerable numbers of patients with focal nephritis Many of the older clinicians did not differentiate adequately between diffuse glomerulonephritis and other forms of Bright s disease This was particularly true of the renal complications of erysipelas typhoid fever various forms of sepsis pneumonia and other infections which were usually designated as acute nephritis or ' hemorrhagic nephritis without any attempt to make the important differentiation between focal nephritis and diffuse glomerulonephritis In New York City, in recent years the importance of scarlet fever in the etiology of acute glomerulonephritis has become far less than it was previously

Tonsillitis and Other Varieties of Sore Throat —The foregoing table and discussion emphasize the great importance of demonstrable infections of the lymphoid tissue of the throat particularly tonsillitis in the etiology of glomerulonephritis It is probable moreover, that a considerable proportion of the cases of unascertained etiology and of those following exposure to cold has been preceded by mild throat infections which did not attract

attention The important role played by infections of the tonsillar ring in the etiology of glomerulonephritis has been emphasized adequately only in recent years though in 1880 Kannenberg[3] described cases of acute nephritis following tonsillitis and peritonsillar abscess As mentioned above, at least 90 per cent of the cases of glomerulonephritis in adults seen by the writer in New York City follow sore throat

While the glomerulonephritis rarely sets in while the inflammation in the throat is still severe more often the renal complication first becomes evident a few days or even a week or two after subsidence of the angina thus showing an analogy to the course of events in scarlet fever Glomerulonephritis may follow very mild attacks of tonsillitis as well as severe ones and peritonsillar abscess However Seegal and Earle[2] found that the antecedent infection is more often severe (deep) in glomerulonephritis than in rheumatic fever When glomerulonephritis occurs in the presence of chronically diseased tonsils it is usually difficult to decide whether the latter were concerned in the genesis of the renal condition Glomerulonephritis may follow tonsillitis which has been treated promptly with a sulfonamide penicillin or another antibiotic Whether such treatment diminishes the incidence of the renal complication has not been established

The proportion of the totality of cases of tonsillitis that is complicated by clinically evident glomerulonephritis is extremely small Thus Kaiser-Petersen and Schwab[4] observed but 10 instances of acute glomerulonephritis in 479 cases of angina * Slight proteinuria at the height of the fever is of course much more common but differs in no wise from 'febrile albuminuria' in other pyrexias Focal nephritis may also occur (Chapter 23)

The close but as yet totally unexplained relation of tonsillar infection to glomerulonephritis is further illustrated by the following two facts (1) Acute glomerulonephritis may occur after tonsillectomy Hill[5] mentions 2 such cases and I have made the same observations (2) When infected tonsils are removed in a patient with subsiding glomerulonephritis there is often an exacerbation of the hematuria and less frequently of other symptoms several authors mention this and I have seen it a number of times However the same phenomenon may occur after operation on other infectious foci and most often there is little immediate change in the urine following tonsillectomy

Scarlet Fever —Proteinuria is encountered at the height of the fever in a large proportion of patients with scarlatina to pass off with defervescence Focal nephritis also occurs in a small fraction of the cases during the febrile period Septic cases may be complicated usually during the first week but sometimes later by acute interstitial nephritis But by far the most important of the renal complications of scarlet fever is acute glomerulonephritis It is often aptly termed postscarlatinal glomerulonephritis for it occurs almost invariably from the second to the sixth week of the disease after the symptoms have passed away and desquamation is taking place It may occur as late as the seventh week The most common time

* However subclinical renal implication is probably far more common The writer has seen several instances of acute tonsillitis in which daily examination of the urine revealed minimal proteinuria cylindruria and hematuria a week or so after defervescence these proved evanescent and there were no symptoms of renal disease

of onset is between the eighteenth and twenty-second days Barasch[10] observed the following dates of onset in 121 cases of postscarlatinal glomerulonephritis

Day of scarlatina	*No of cases*
5 to 9	1
10 to 14	10
15 to 19	26
20 to 24	44
25 to 29	20
30 to 34	10
35 to 39	7
40 to 45	3

Postscarlatinal glomerulonephritis is thus one of the group of manifestations of scarlet fever that generally appears after the disease is seemingly over The intimate interrelations of these late affections have been especially studied by Schick[11] and Pospischill[12] and the entire group termed by the latter the second sickness The manifestations of the second sickness are lymphadenitis, glomerulonephritis fever without readily discernible cause, angina relapse of the scarlet fever endocarditis synovitis and erythema (Jochmann[13]) These occur individually or in any combination The most important of them is glomerulonephritis

The incidence of postscarlatinal glomerulonephritis apparently varies enormously with the *genius epidemicus* Some years it is much more than others McCrae[14] found well marked urinary changes after the febrile period in 10 per cent of 1034 cases of scarlet fever, about 5 per cent showed sufficiently marked abnormalities to warrant the diagnosis of nephritis and in about 2 per cent there were extrarenal manifestations of nephritis Rolly[15] observed postscarlatinal glomerulonephritis in 7 per cent of 1400 cases Steiner and Johannessen[16] studied an epidemic of scarlet fever in which over 70 per cent of the cases were complicated by nephritis On the other hand, Caiger[17] found nephritis in only 3 32 per cent of 2078 cases of scarlet fever Friedländer[18] encountered postscarlatinal glomerulonephritis in 42 of 229 necropsies on scarlet fever patients Scarlet fever is much less apt to be followed by glomerulonephritis in adults than in children thus Caiger found the incidence of nephritis in scarlet fever to be 3 6 per cent in children under fifteen years of age but only about 0 75 per cent in patients over that age In recent years the incidence of postscarlatinal glomerulonephritis in New York City has been very low and this seems to have been true in various parts of the United States Thus Lucchesi and Bowman[19] found that nephritis complicated only 1 26 per cent of 5377 cases of scarlet fever

This great decrease in the incidence of postscarlatinal glomerulonephritis in recent years has been noted in various parts of the world It is not alone if at all due to improvements in therapy for it antedated the introduction of antitoxin sulfonamides and penicillin The decline may be correlated in some way with the far lesser severity of scarlet fever in recent decades but nephritis may follow very mild scarlatina The possibility exists that the lesser incidence of nephritis may result from a change in the

type of streptococcus producing scarlet fever Nevertheless, in some years the great frequency of scarlet fever renders it an important cause of acute glomerulonephritis in children In fact, in former years it was much the most common cause of glomerulonephritis in children Thus in the London Hospital for Sick Children admitting all varieties of diseases, Dickinson[9] found that 75 of 89 cases of nephritis were due to scarlet fever In New York City at present, the proportion of cases of glomerular nephritis in children due to scarlatina is far less In fact in recent years there have been few cases of clinically evident post scarlatinal glomerulonephritis Hirschberg and Saucharewa[21] find that the liability to renal complication in children with scarlet fever increases with age the incidence in children between the ages of eight and twelve years was 23 2 per cent while below one year it was but 4 3 per cent In adults scarlatina is much less important as a cause of acute glomerulonephritis Dickinson finding but 7 of 50 cases due to it Caiger states that children of both sexes are equally liable but that among adults males are more frequently affected

Lyttle[22] showed that the tendency to renal implication following scarlet fever is a very general one even though frank glomerulonephritis develops nowadays in an extremely small minority of the cases By using the Addis sediment count he found that all of 14 children had moderate transient increases in the excretion of protein and formed elements in the urine between eight and forty five days after the onset of scarlet fever

Glomerulonephritis may follow mild cases of scarlet fever quite as well as severe ones Sometimes the preceding scarlet fever is so mild as to be entirely overlooked only the presence of typical desquamation in a patient with acute glomerulonephritis reveals the origin of the renal mischief Graves[2] tells of an instance in which all but one of the children of a physician contracted scarlet fever The seemingly uninfected child nursed the others without showing any evidence of the disease until they were convalescent and left for the country when she became dropsical

Subacute Bacterial Endocarditis —Baehr and Lande[24] found diffuse glomerulonephritis in 9 of 77 necropsies on individuals with subacute bacterial endocarditis from which they conclude that glomerulonephritis complicates this disease in a higher proportion of cases than any other ailment with the possible exception of scarlet fever Indeed lesser degrees of cellular proliferation within the glomeruli not meriting the designation glomerulonephritis are even more common in subacute bacterial endocarditis Christian[25] found them in 80 per cent of his cases Baehr and Lande were of course careful to differentiate glomerulonephritis from focal glomerular lesions which were so common in subacute bacterial endocarditis in pre penicillin days Of their 9 cases of glomerulonephritis 2 were acute and 7 chronic Libman[26] observed that cases which come under observation in the bacteria free stage present glomerular nephritis at least fifteen times as often as it occurs in the active stage of the disease an important difference (see page 555) that is borne out by the extensive investigations of Baehr Libman[1] pointed out in his original description that the clinical picture of the bacteria free stage of subacute bacterial endocarditis is often completely dominated by the manifestations of glomerulonephritis It will be mentioned below that glomerulonephritis may occur

also in subacute bacterial endocarditis due to influenza bacilli pneumococci or gonococci

Antibiotics seem almost to have eliminated glomerulonephritis as a manifestation of subacute bacterial endocarditis Spain and King [8] report that while diffuse glomerulonephritis was found at necropsy in 33 per cent of 52 untreated cases, it was not found in any of 25 treated cases I have not seen glomerulonephritis in subacute bacterial endocarditis in the past two or three years

Pneumonia — Though febrile proteinuria is common in lobar pneumonia glomerulonephritis is an extremely rare complication For statistics in the incidence of glomerulonephritis in lobar pneumonia it is necessary to rely on older observations because of the remarkable therapeutic efficacy of sulfonamides and penicillin in pneumococcic pulmonary infections Nauwerck encountered acute nephritis in 2 3 per cent of 550 cases of primary lobar pneumonia Fraenkel and Reiche [9] in 0 6 per cent of 956 cases and West[30] not once in 100 cases Judging by the descriptions of the cases, in which edema is generally absent only a minority is true glomerulonephritis the larger part evidently being focal nephritis Blackman[31] described 10 examples of nephropathies in children secondary to pneumococcal infections which he regards as "pneumococcal lipoid nephrosis," but at least some of which would fall within the concept of glomerular nephritis as used in this book and by most contemporary clinicians In a careful study of the kidneys in lobar pneumonia using accurate methods Goldring[32] encountered only 2 certain instances of glomerulonephritis in 44 adult patients Seegal[33] observed only 7 cases of glomerular nephritis in 1007 patients with pneumococcic lobar pneumonia While most of the anatomical findings are likewise those of focal nephritis Nauwerck and von Kahlden[34] found glomerulonephritis at necropsy In other cases, only tubular lesions are found Blackman[3] has produced glomerular lesions by the repeated injection of pneumococcal autolysate but the identity of the changes with those of human glomerulonephritis is still *sub judice* However that pneumococci can cause true glomerulonephritis would seem to be demonstrated by a case of subacute bacterial endocarditis due to pneumococcus Type II, observed at Mount Sinai Hospital in which typical subacute glomerulonephritis was found at necropsy Nauwerck found pneumococci in large numbers in the kidney of a patient who succumbed to glomerulonephritis complicating pneumonia but this is not significant for they may be present in the absence of renal disease It need scarcely be added that pneumonia complicates glomerulonephritis far more commonly than the reverse such complicating pulmonary inflammations are generally bronchopneumonic in type but may be typical lobar pneumonia I have not seen glomerulonephritis complicating pneumonia since antibiotics came into use

In the rare cases in which glomerulonephritis does complicate pneumonia it may occur either at the height of the disease or after the crisis In Seegal s cases, glomerulonephritis generally appeared two or three weeks after the onset of the pneumonia

Using the urea clearance test, Goldring[32] found excellent renal function to be the rule during the acute stage of the disease Only 2 of 13 patients studied developed impairment of renal function during the acute stage and

these returned to normal in less than a week. Similar results were obtained by McIntosh and Reiman[36] and by Farr and Abernethy.[37] The latter investigators observed that in patients under forty years the urea clearance generally rises well above normal and stays at that level for about a month, while in older individuals there is little change in the clearance.

Pyogenic Infections.—Various pyogenic infections (osteomyelitis, empyema, sinusitis, otitis media, mastoiditis, furunculosis, etc.) are followed in rare instances by acute glomerulonephritis. The figures given by Longcope indicate that infections of the paranasal sinuses may be of etiological importance in a not inconsiderable number of instances of acute glomerulonephritis.

The incidence after infections of the skin seems to be higher than after the others. Acute glomerulonephritis has often been observed after impetigo, infected burns, and skin diseases with pruritus, such as eczema and scabies, in which secondary infection of scratch wounds is presumably responsible. It appears that the cutaneous infections causing glomerulonephritis are streptococcic. Futcher[38] isolated beta hemolytic streptococci from 7 of 11 cutaneous lesions complicated by glomerulonephritis, and 2 of the 4 patients who did not have cultures had erysipelas. Even in impetigo, the cutaneous infection most often followed by glomerulonephritis, the primary organism seems to be a streptococcus. A large number of cases of "hemorrhagic nephritis" has been reported following the application of medicaments (naphthol, turpentine, chrysarobin, etc.) to skin lesions. Most of these apparently are not true glomerulonephritides; if any are, the factor of secondary infection as the cause of the renal complication would have to be excluded. Peculiarly enough, the streptococcus infection *par excellence* of the skin, erysipelas, is very rarely complicated by glomerulonephritis. Munk[39] did not find a single instance in almost 100 cases of erysipelas. Focal nephritis is less rare in erysipelas.

Operations on infected foci are on rare occasions quickly followed by acute glomerulonephritis. It was mentioned above that Hill reported 2 such cases following tonsillectomy. I have seen acute glomerulonephritis set in a few days after the extraction of several infected teeth.

In at least most of the rare instances in which pyogenic infections are followed by glomerulonephritis, the microorganism is a hemolytic streptococcus. It seems to be extremely rare for staphylococcus infections to result in glomerulonephritis, if indeed it occurs at all. The cases published by Rigdon[40] do not prove that staphylococcus infections can result in glomerulonephritis in the sense that the term is used in this book.

Purpuras.—Johnson[41] noted long ago that nephritis with edema may follow purpura. In Osler's[42] classic papers on the erythema group, in which he included simple erythema, erythema exudativum, herpes iris, erythema nodosum, certain of the purpuras, urticaria and angioneurotic edema, he emphasized the great frequency with which the severe cases of this group—now known to be heterogeneous—are complicated by acute nephritis. Of 29 cases which he reported, 14 had the renal complication, with 5 deaths from uremia. Two had dropsy. In the 14 cases with nephritis, in 4 purpura alone was present, in 3 purpura and urticaria, in 2 purpura, urticaria and erythema, in 1 purpura, erythema and edema, in 1 at various

times, purpura, simple erythema, urticaria, and localized edema, in 1, edema and erythema, in 2, purpura and erythema." He never met with acute nephritis in pure cases of angioneurotic edema. It is seen that of the 14 patients with acute nephritis, 13 had purpura, while the other cutaneous manifestations varied greatly. Osler states that the nephritis usually appears at the height of the skin lesions, though it may follow a week or more, and once even a couple of months later. Similar series of cases of acute glomerulonephritis complicating purpuras particularly with visceral manifestations have been reported by Nobecourt,[43] Lippmann[44] and many others. I have not seen glomerulonephritis in thrombopenic purpura but only in the types of hemorrhagic diathesis in which there is reason to assume primary capillary damage. The renal lesion is, perhaps, to be regarded as part of the widespread capillary disease developing in all probability on an allergic basis.

Glomerulonephritis complicating the purpuric diseases may pass into the chronic stage. Thus, Watson[45] observed a patient who died of a renal complication in arthritic purpura; at necropsy, MacCallum found subacute extracapillary glomerulonephritis. Osler mentions a patient who developed acute nephritis during an attack of visceral purpura at the age of twelve years, which went into the chronic form with hypertension and hypertensive neuroretinopathy. It seems that the proportion of these cases that becomes chronic is not inconsiderable.

Rheumatic Fever.—In the febrile stages of rheumatic fever, as in other pyrexias, Goldring and Wyckoff[46] have shown by careful methods that there is increased elimination of protein, casts and cellular elements in the urine. But true glomerulonephritis complicates rheumatic fever in only an extremely small proportion of the cases. In several thousand cases of rheumatic fever collected from the literature Rolly[47] states that acute nephritis occurred in but 0.67 per cent; this complication was present in 16 of 2652 cases of rheumatic fever which he personally observed. Evidently most of even this small proportion of acute nephritides were not instances of true glomerulonephritis, for edema is rarely mentioned among the symptoms, though it was present in the case reported by Bartels.[48] In his paper on the characterization of the various forms of endocarditis, Libman[49] pointed out that glomerulonephritis was absent in the cases proved to be due to rheumatic fever by the presence of Aschoff bodies in the myocardium. There were no instances of glomerulonephritis in the above mentioned series of Goldring and Wyckoff. Baehr and Schifrin[50] made a careful study of the kidneys of 235 patients who succumbed with rheumatic heart disease, 118 during the stage of acute rheumatic fever. Glomerulonephritis was present in only 3 instances. Of these, 1 was an old secondary contracted kidney probably dating back to early life, antecedent to the rheumatic fever, and another caused no clinical manifestations; in the third a bout of rheumatic fever was complicated by glomerulonephritis which terminated in uremia. In 153 necropsies on patients succumbing to rheumatic heart disease Hutton and Brown[51] found no diffuse glomerulonephritis. There were 3 instances of focal glomerulitis and arteritis and 1 of diffuse obstructive vascular disease in the kidneys, with renal insufficiency dominating the clinical picture in 2 of the patients. During a period of about five years I

saw anatomically typical acute glomerulonephritis in only 2 patients who died during active rheumatic fever. Rheumatic fever and glomerulonephritis thus occur together so rarely as to suggest fortuitous association.

Libman-Sacks Disease (Disseminated Lupus Erythematosus) —Glomerular lesions are the rule and death from uremia common in the remarkable chronic pyrexia first differentiated by Libman and Sacks[52] under the name of atypical verrucous endocarditis and since shown by Klemperer, Pollack and Baehr[53] to be characterized morphologically by widespread changes in collagenous tissue. However in only a small minority of the cases are the glomerular lesions classical glomerulonephritis identical with those of the disease described in this chapter (p 547). Klemperer et al found glomerulonephritis in only 2 of their 21 carefully studied cases and Bell in 2 of 21.



FIG 23 —Glomerulus from the kidney of a 34 year-old woman with disseminated lupus erythematosus, clinical onset three years before with a rash following exposure to sun. The walls of the capillaries are thickened by an eosinophilic hyaline deposit which imparts to a few the "wire loop" appearance. Some of the lumens appear to contain thrombi (last NPN 74 mg per cent)

Wire Loop Lesions —Far more common than classical glomerulonephritis are the alterations in the glomerular loops described by Baehr, Klemperer and Schifrin[54] under the designation of wire loop lesions. They found these changes in 13 of 23 cases. The incidence of wire loop lesions was less than this in the cases studied by Stickney and Keith[55] who found the kidneys abnormal in only 7 of 15 cases and observed increase in the number of endothelial cells as the most common lesion. The lesions were called wire loop because the walls of the involved loops are thickened and hyaline and appear rigid so that they resemble (rather distantly) loops of bent wire. The thickened walls stain deeply with eosin; in Mallory preparations red staining is more common than blue but both may coexist. Specific amyloid stains are negative. The thickening involves the basement membrane and may be diffuse or

segmental A varying proportion of loops in a glomerulus and of glomeruli in a kidney may be involved Some of the thickened loops become necrotic and others are occluded by what may be either extreme thickening of the wall or hyaline thrombosis Klemperer and his associates found that necrosis of loops occurs also in the absence of wire loop lesions and is more common than the latter The appearance designated as the wire loop lesion is not specific for Libman-Sacks disease, Klemperer *et al*, observed it in 5 of 43 cases of subacute and chronic glomerulonephritis, but here it was accompanied by proliferative and exudative changes Wire loop lesions have been observed in scleroderma but are rare in this disease (Allen)[46] Similar appearances may be encountered in the toxemia of pregnancy and the arteriolosclerotic kidney of essential hypertension

The tubules in kidneys the site of wire loop lesions are generally not strikingly altered, there are often moderate lipid and other regressive changes, and casts may be seen Fibrinoid degeneration and necrosis of arterioles and arteries may be present, as may periarterial cellular infiltration

The nature of the glomerular lesions of Libman-Sacks disease and their relation to classical glomerulonephritis are obscure It is possible, but purely hypothetical, that the thickening of the loops results in some obscure fashion from the hyperglobulinemia, notably gamma hyperglobulinemia (Walker and Benditt[57]), that is present

The renal lesions of disseminated lupus erythematosus result in proteinuria cylindruria and hematuria of varying degrees Pus clumps are common and the cases sometimes pass for pyelitis for a considerable time Krupp[58] has pointed out that the urinary sediment in disseminated lupus may be remarkably variegated containing at the same time red blood cells, red cell casts oval fat bodies fatty casts, and broad casts Impairment of renal function with hyposthenuria and azotemia may develop and many of the patients succumb to uremia Hypoproteinemia and edema are common and in some of the cases hypercholesteremia completes the nephrotic syndrome Hypertension is exceptional and rarely more than light I have not seen hypertensive retinopathy Sometimes it is the appearance of proteinuria and impairment of renal function in an obscure fever that first leads to the suspicion of Libman-Sacks disease

Erythema Nodosum —On extremely rare occasions glomerulonephritis appears in patients with erythema nodosum Wallgren[59] observed 3 such cases and found by Addis counts that over one quarter of 88 children with erythema nodosum had an increase in the number of red blood cells in the urine at the height of the eruption Since erythema nodosum is probably a nonspecific allergic manifestations and many of the patients have beta hemolytic streptococci in the throat, the occasional occurrence of glomerular changes is not surprising

Influenza —Influenza is complicated by acute glomerulonephritis on rare occasions That the influenza bacillus itself can cause this renal lesion is shown by Libman's[49] observation that subacute bacterial endocarditis due to the bacillus of Pfeiffer may be complicated by glomerulonephritis In one of these cases, in which influenza bacilli were cultured from the blood I observed typical subacute glomerulonephritis In the unusual cases of the last influenza epidemic in which glomerulonephritis developed it was not clear to which microorganism the renal complication was attributable Widal, Lemierre and Vallery-Radot[60] state that the kidney was involved more often in the epidemic of 1889, on both occasions, the renal disease became chronic in some instances

Tuberculosis.—In incipient tuberculous patients with fever protein may be found in the urine but this febrile proteinuria seems to be less common than in diseases with high and continuous pyrexia as typhoid fever and pneumonia Maurice Fishberg[61] found proteinuria in but 9 of 100 patients with early but active pulmonary tuberculosis Teissier[62] and other French clinicians describe an *albuminurie prétuberculeuse* but there is no evidence that proteinuria precedes the onset of tuberculosis with notable frequency In advanced pulmonary tuberculosis and extensive tubercle of other organs proteinuria is very common and of various origins It may result from the fever amyloid disease tuberculosis of the kidneys cardiac insufficiency in cases of fibroid phthisis or rarely glomerulonephritis or chronic nephrosis

Nephritis has been stated by many authors to be a common complication of pulmonary phthisis but this is an error due to basing the diagnosis of nephritis on the presence of proteinuria or edema We have just mentioned the various causes of proteinuria in tuberculous subjects Likewise edema in such patients is generally not nephritic but much more often results from amyloid disease or cardiac failure and in terminal cases dropsical swelling is often seen purely as a manifestation of the hypoproteinemia of undernutrition Less rarely than is generally realized edema in the last stages of pulmonary tuberculosis is due to venous thromboses particularly of the veins of the lower extremities

True glomerulonephritis is a very rare complication of pulmonary tuberculosis having been found by Holten[63] in but 13 of 2800 admissions He observed it in incipient cases as well as advanced However I have seen fairly well marked reactive changes in the glomeruli with greater frequency than this but there was usually no clear-cut evidence during life of glomerulonephritis When glomerulonephritis does complicate active pulmonary tuberculosis it is notable that arterial hypertension is usually lacking or slight presumably because of the hypoplastic cardiovascular apparatus of most tuberculous patients and the general weakness Edema and uremia occur but are rare I have seen hypertensive retinal lesions only twice both times in patients with fibroid phthisis

It has not been demonstrated whether the glomerulonephritis of tuberculous patients is due to the toxic products of the tubercle bacillus itself to secondary invaders in cavities or is entirely independent of the tuberculous process Quite possibly each of these three modes of origin holds in different cases Long and Finner[64] have brought forward evidence that the products of the tubercle bacillus can injure the glomeruli for they were able to produce glomerular lesions experimentally by injecting tuberculin into the renal artery of swine with mild tuberculosis

Trench Nephritis (*War Nephritis*).—During World War I large numbers of cases of acute glomerulonephritis occurred among the men on both sides of the front A similar high incidence of renal disease was observed in the Civil War from March 1862 to March 1863 but not in the Franco German Spanish American Boer or Russo Japanese wars (Langdon Brown[65]) There were few cases during the first year of the war but in the course of 1915 the incidence of the disease assumed almost epidemic proportions among the Allied troops On the German side likewise the

segmental A varying proportion of loops in a glomerulus and of glomeruli in a kidney may be involved Some of the thickened loops become necrotic and others are occluded by what may be either extreme thickening of the wall or hyaline thrombosis Klemperer and his associates found that necrosis of loops occurs also in the absence of wire loop lesions and is more common than the latter The appearance designated as the wire loop lesion is not specific for Libman-Sacks disease, Klemperer *et al*, observed it in 5 of 43 cases of subacute and chronic glomerulonephritis, but here it was accompanied by proliferative and exudative changes Wire loop lesions have been observed in scleroderma but are rare in this disease (Allen)[56] Similar appearances may be encountered in the toxemia of pregnancy and the arteriolosclerotic kidney of essential hypertension

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The renal lesions of disseminated lupus erythematosus result in proteinuria, cylindruria and hematuria of varying degrees Pus clumps are common and the cases sometimes pass for pyelitis for a considerable time Krupp[58] has pointed out that the urinary sediment in disseminated lupus may be remarkably variegated containing at the same time red blood cells, red cell casts, oval fat bodies fatty casts, and broad casts Impairment of renal function with hyposthenuria and azotemia may develop and many of the patients succumb to uremia Hypoprotein emia and edema are common and in some of the cases hypercholesteremia completes the nephrotic syndrome Hypertension is exceptional and rarely more than light I have not seen hypertensive retinopathy Sometimes it is the appearance of proteinuria and impairment of renal function in an obscure fever that first leads to the suspicion of Libman-Sacks disease

Erythema Nodosum —On extremely rare occasions glomerulonephritis appears in patients with erythema nodosum Wallgren[59] observed 3 such cases and found by Addis counts that over one quarter of 88 children with erythema nodosum had an increase in the number of red blood cells in the urine at the height of the eruption Since erythema nodosum is probably a nonspecific allergic manifestations and many of the patients have beta hemolytic streptococci in the throat, the occasional occurrence of glomer ular changes is not surprising

Influenza —Influenza is complicated by acute glomerulonephritis on rare occasions That the influenza bacillus itself can cause this renal lesion is shown by Libman s[49] observation that subacute bacterial endocarditis due to the bacillus of Pfeiffer may be complicated by glomerulonephritis In one of these cases in which influenza bacilli were cultured from the blood I observed typical subacute glomerulonephritis In the unusual cases of the last influenza epidemic in which glomerulonephritis developed, it was not clear to which microorganism the renal complication was attributable Widal Lemierre and Vallery-Radot[60] state that the kidney was involved more often in the epidemic of 1889 on both occasions the renal disease became chronic in some instances

Tuberculosis —In incipient tuberculous patients with fever protein may be found in the urine but this febrile proteinuria seems to be less common than in diseases with high and continuous pyrexia as typhoid fever and pneumonia Maurice Fishberg[61] found proteinuria in but 9 of 100 patients with early but active pulmonary tuberculosis Leisser[62] and other French clinicians describe an *albuminurie prétuberculeuse* but there is no evidence that proteinuria precedes the onset of tuberculosis with notable frequency In advanced pulmonary tuberculosis and extensive tubercle of other organs proteinuria is very common and of various origins It may result from the fever amyloid disease tuberculosis of the kidneys cardiac insufficiency in cases of fibroid phthisis or rarely glomerulonephritis or chronic nephrosis

Nephritis has been stated by many authors to be a common complication of pulmonary phthisis but this is an error due to basing the diagnosis of nephritis on the presence of proteinuria or edema We have just mentioned the various causes of proteinuria in tuberculous subjects Likewise edema in such patients is generally not nephritic but much more often results from amyloid disease or cardiac failure and in terminal cases dropsical swelling is often seen purely as a manifestation of the hypoproteinemia of undernutrition Less rarely than is generally realized edema in the last stages of pulmonary tuberculosis is due to venous thromboses particularly of the veins of the lower extremities

True glomerulonephritis is a very rare complication of pulmonary tuberculosis having been found by Holten[63] in but 15 of 2800 admissions He observed it in incipient cases as well as advanced However I have seen fairly well marked reactive changes in the glomeruli with greater frequency than this but there was usually no clear-cut evidence during life of glomerulonephritis When glomerulonephritis does complicate active pulmonary tuberculosis it is notable that arterial hypertension is usually lacking or slight presumably because of the hypoplastic cardiovascular apparatus of most tuberculous patients and the general weakness Edema and uremia occur but are rare I have seen hypertensive retinal lesions only twice both times in patients with fibroid phthisis

It has not been demonstrated whether the glomerulonephritis of tuberculous patients is due to the toxic products of the tubercle bacillus itself to secondary invaders in cavities or is entirely independent of the tuberculous process Quite possibly each of these three modes of origin holds in different cases Long and Finner[64] have brought forward evidence that the products of the tubercle bacillus can injure the glomeruli for they were able to produce glomerular lesions experimentally by injecting tuberculin into the renal artery of swine with mild tuberculosis

Trench Nephritis (War Nephritis) —During World War I large numbers of cases of acute glomerulonephritis occurred among the men on both sides of the front A similar high incidence of renal disease was observed in the Civil War from March 1862 to March 1863 but not in the Franco German Spanish American Boer or Russo-Japanese wars (Langdon Brown[65]) There were few cases during the first year of the war but in the course of 1915 the incidence of the disease assumed almost epidemic proportions among the Allied troops On the German side likewise the

segmental A varying proportion of loops in a glomerulus and of glomeruli in a kidney may be involved Some of the thickened loops become necrotic and others are occluded by what may be either extreme thickening of the wall or hyaline thrombosis Klemperer and his associates found that necrosis of loops occurs also in the absence of wire loop lesions and is more common than the latter The appearance designated as the wire loop lesion is not specific for Libman-Sacks disease, Klemperer *et al*, observed it in 5 of 43 cases of subacute and chronic glomerulonephritis, but here it was accompanied by proliferative and exudative changes Wire loop lesions have been observed in scleroderma but are rare in this disease (Allen) [56] Similar appearances may be encountered in the toxemia of pregnancy and the arteriolosclerotic kidney of essential hypertension

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high incidence of acute glomerulonephritis started in the middle of 1915 and declined after 1916 The disease was largely confined to the men actually fighting in the trenches, the other units of the armies and the surrounding population escaping almost entirely Men of all ages were equally affected (Maclean[66]), but some German observers state that the disease was more severe in the older soldiers

In World War II, acute glomerulonephritis seems to have been far less common among the American and British troops than in 1914-18 (a detailed study of 63 cases in Africa and Italy has been published by Brod[67]) The decreased incidence may well have been correlated with less trench warfare The Germans apparently had considerable "war nephritis" in their winter campaigns in Russia (cf Pilgersdorfer) [68]

Despite extensive investigations (which will be found summarized in Maclean's excellent communication to the Medical Research Committee) the etiology of trench nephritis during World War I was not then regarded as completely elucidated The fact that the disease was confined to the men in the trenches made it probable that cold exposure and exhaustion played an important role through predisposing to infection The disease occurred almost as often in summer as in winter, but men in the trenches are subject to exposure on damp summer nights

The general manifestations of the disease—epidemic occurrence generally febrile onset, bronchitic phenomena frequent splenic enlargement—all pointed to a primarily infectious origin of the disease Nevertheless the microorganism responsible was not discovered Wilson[69] examined bacteriologically the throat, blood urine and feces in 100 cases without conclusive results Streptococci spirochetes filtrible viruses and many other organisms were blamed by various investigators Maclean and others believed the virus might be transmitted by the louse as in trench fever for the disease was almost entirely restricted to the men in the trenches but there was no convincing evidence for this view The theories put forward that the disease was due to metallic poisoning avitaminosis drinking of chlorinated water etc were little more than speculations

From what is now known of the etiology of acute glomerulonephritis and in view of the identity of the clinical and anatomical pictures of trench nephritis and acute glomerulonephritis in civilian life there seems every reason to believe that the etiology is the same in both forms and that the great frequency of acute glomerulonephritis in the trench warfare of World War I was a result of the exposure of life in the trenches predisposing to streptococcic throat infections

The pathological investigations of Dunn and MacNee [70] Keith and Thomson [71] Herxheimer [2] and others showed conclusively that trench nephritis was a typical acute diffuse glomerulonephritis the lesions in the kidney being practically identical with those which are so well known in acute glomerulonephritis in times of peace In fact the cases of war nephritis offered the best opportunity ever available for studying the early stages of acute glomerulonephritis and the anatomical findings will be discussed further below

Other Infections —Acute renal disease with hemorrhagic urine may supervene in almost all acute infections—typhoid fever, measles smallpox

chickenpox mumps typhus fever cerebrospinal fever gonorrhea bacillary dysentery and many others It seems however that in the vast majority of instances *true glomerulonephritis is not present* but the renal complication consists in focal nephritis Even in the rare cases in which there is true glomerulonephritis it is not known how often this is due to the specific germ of the disease for secondary infection (most probably with streptococci) may be responsible for the glomerulonephritis *In some instances* the seemingly acute glomerulonephritis in the course of one of these diseases is really an acute exacerbation of a chronic process reawakened by the disease

On the other hand in rare instances of certain chronic *bacteremias* the *evidence* seems strong that the germ of the disease in question is responsible for the renal mischief This is especially true in protracted gonorrheal bacteremia Longcope mentions cases of glomerulonephritis due to the gonococcus Oettinger Marie and Morance[73] have described the occurrence of glomerulonephritis in gonorrheal sepsis and I have several times seen glomerulonephritis complicate bacterial endocarditis due to the gonococcus Gandy and Geguignand[74] as well as others have observed glomerulonephritis develop *in the course* of chronic meningococcemia These *forms* of acute glomerulonephritis have practically disappeared since the introduction of antibiotics

Judging by the literature *malarial fever* a disease with which I have little personal experience is not uncommonly complicated by glomerulonephritis Descriptions of cases with edema impaired concentrating ability of the kidneys and high blood pressure will be found in the monograph of Giglioli[75] His patients were greatly helped by quinine treatment provided they were not too far advanced at the time the therapy was instituted The renal complication occurred particularly in long standing cases Edema in chronic malaria may of course be purely cachectic and without relation to glomerulonephritis (see also p 608)

In the course of his important anatomical investigations Bell[76] has published observations which he interprets as indicating that glomerular changes of the same nature as but of less severity than those in typical glomerulonephritis occur frequently in a wide variety of infections (puerperal sepsis tuberculosis etc) in which clinical glomerulonephritis is extremely rare Baehr points out however that the fact that the glomerulonephritis of the clinician is so rare in these diseases bespeaks a fundamental difference between Bell s subclinical glomerulitis and clinical glomerulonephritis Moreover the development of chronic renal disease from the acute glomerular lesions in the diseases in question is practically unknown which again points towards a difference between them and the glomerulonephritis following sore throat or scarlet fever And the glomerulitis which may complicate almost any infection—here called focal nephritis—and is rarely clinically *significant* occurs at the height of the infection while glomerulonephritis appears after resistance has been developed

Poison Oak and Poison Ivy —Rytand[78] published several cases of acute glomerulonephritis and the nephrotic syndrome in which it seems probable that the renal disease was due to sensitization to poison oak More

recently, Shaffer *et al*[79] observed 2 patients in whom acute glomerulonephritis followed administration of Rhus Toxicodendron toxin for active treatment of poison ivy contact dermatitis These observations are of great interest in connection with the allergic nature of acute glomerulonephritis

Pregnancy —Pregnancy in its relations to acute glomerulonephritis is discussed in Chapter 32

Chemicals —Various chemicals are nephrotoxic However, the lesions produced by these substances are either nephroses or focal nephritis and not true glomerulonephritis I have not seen any case in which definite glomerulonephritis resulted from chemical poisoning and the failure to produce glomerulonephritis experimentally with chemicals seems to point in the same direction

Experimental Glomerulonephritis —The literature of attempts to produce glomerulonephritis experimentally in animals is enormous but the older results were so meager that it seems unnecessary to review them here Summarizing an excellent survey of work prior to 1924 Leiter[80] concluded that 'Chronic glomerulonephritis has not been produced constantly or even frequently in an experimental animal Lesions similar in many points to human glomerulonephritis were produced by Christian[81] and his coworkers, Baehr[82] and others but they cannot be considered as identical with glomerulonephritis as it occurs in man

In view of the predominant role of streptococcal infections in the etiology of glomerulonephritis a number of attempts have been made to reproduce the disease in animals by the injection of streptococci and their products Pneumococcal autolysates have also been used With the realization that sensitization plays a fundamental part in the pathogenesis of acute glomerulonephritis attempts were made to reproduce the disease through immunologic mechanisms These have produced clinical pictures and anatomical changes which at least closely simulate human glomerulonephritis To avoid repetition consideration of this work will be postponed to the section on pathogenesis (p 556)

Predisposing Factors — *Age* —The incidence of acute glomerulonephritis at different ages is a function of the frequency at these periods of the infections which it complicates Because of the important role of scarlet fever and angina in the etiology of acute glomerulonephritis it is most common in childhood It may occur during earliest infancy 3 of Clausen's[83] 102 patients with acute glomerulonephritis developed in the first year of life Renme[84] reported 10 cases in infants less than eighteen months of age and I have seen several However before the age of three chronic nephrosis is more common than glomerulonephritis Next to childhood the greatest incidence of the disease is in adolescents and young adults in whom it most commonly follows tonsillitis and other forms of angina Acute glomerulonephritis is rare in the aged but I have once seen the first attack after sixty years of age

A few cases have been observed which indicate that on extremely rare occasions glomerulonephritis develops *in utero (congenital nephritis)* Karsner[85] describes a diffuse proliferative lesion of the glomeruli in an infant who succumbed forty five minutes after birth He also quotes 3

other cases from the literature in 1 of which anasarca develops the day after birth and chronic renal disease was later found at necropsy Thompson[1] found subacute to chronic glomerulonephritis in an infant who succumbed at twenty nine days, the mother had had pharyngitis in the sixth month and the possibility of intrauterine sensitization to organisms in the mother was considered Dr Chester Brown has shown me the kidneys of an infant who died at the age of four months with glomerulonephritis that had already attained the subchronic stage the process must have had its inception either before or shortly after birth

Sex —Dickinson[86] found that of 105 cases in children 58 were in boys and 47 in girls while of 54 cases in adults 33 were in males Murphy and Rastetter[87] and Seegal Seegal and Lyttle[88] found an even greater predominance of males The higher incidence in adult males is perhaps due to their greater exposure to cold and wet with resultant tonsillitis and other infections

Familial Occurrence —A number of instances have been recorded in which multiple cases of glomerulonephritis occurred in the same family, either within a short period of one another or at long intervals Thus Eason *et al* [89] studied a family in which three brothers and a sister developed acute glomerulonephritis within a relatively short period Frostene and Robb[90] observed a familial epidemic in which in quick sequence an upper respiratory infection was followed by glomerulonephritis in 6 of 10 brothers and sisters Rinkoff *et al* [91] followed three brothers who succumbed to uremia in all of whom necropsy revealed chronic glomerulonephritis I have also followed a family in which three brothers at long intervals developed glomerulonephritis which became chronic However in my experience the familial occurrence of multiple cases of glomerulonephritis has been extremely rare When they do occur one must evaluate the relative importance of coincidence of a familial predisposition perhaps on the basis of allergy or of a common throat infection by a particular type of streptococcus (p 546)

Epidemic Occurrence —Epidemic occurrence of acute glomerulonephritis was observed during World War I as the so-called trench nephritis Epidemics apparently small of the disease were noted in civil life by Tallqvist [92] An epidemic of acute glomerulonephritis was observed in Amsterdam by Formijne [93] and of 17 cases within three months in a mental hospital by Molony [94] In certain years postscarlatinal glomerulonephritis occurs in a far higher proportion of cases of scarlatina than in others (p 532) In New York City the number of cases of acute glomerulonephritis following sore throat varies greatly from year to year In recent years it has been extremely low but during the winter of 1952-53 I observed a much larger number of cases The first explanation of such variations that comes to mind is changes in the type of infecting streptococci

The Role of Cold —Since the time of Christison[95] and Rayer [96] cold has been highly esteemed as an etiological factor in renal disease The combination of cold and wet as being drenched in a cold rain wet feet in cold weather or falling into water seems particularly apt to incite acute glomerulonephritis Exposure to cold when intoxicated is often mentioned in the older literature as being followed by renal disease In New York

City I have observed that glomerulonephritis is more common in individuals whose occupation exposes them to inclement weather and in the children of the poor But since the advent of the bacteriological era, it has become more and more evident that cold, wetting and other varieties of exposure do not in themselves produce glomerulonephritis, which is always primarily the result of an infection In the large majority of patients in whom there is a history of exposure to cold previous to the development of acute glomerulonephritis, sore throat or other evidence of respiratory infection is present But even if angina, rhinitis, sinusitis, etc are not demonstrable infection has doubtless occurred and subsided before the renal disease became evident, there is usually a period of about ten days between the sore throat and the appearance of manifestations of glomerulonephritis In typical instances of glomerulonephritis following exposure, streptococci have been demonstrated in the urine (Luedke [97] Loehlein[98]) even though sore throat or another infectious focus was not observed The changes in the kidneys are identical in those cases of acute glomerulonephritis with a definite history of antecedent infection and in those in which this is not obtained It seems definite, therefore that the renal disease in the latter group also results from an infection and that cold or other exposure participates through creating a predisposition to this infection

The experiments of Mudd and Grant[106] are of interest in this connection They found by accurate methods that 'chilling of the body surface causes reflex vasoconstriction and ischemia in the mucous membranes of the palate faucial tonsils oro pharynx and naso pharynx They believe it not improbable that the ischemia of the mucous membrane resulting from cutaneous chilling might so disturb the equilibrium between the host and the bacteria in the tonsillar crypts and folds of the pharyngeal mucosa as to excite infection A working hypothesis of the role of cold in predisposing to acute glomerulonephritis would therefore be that the reflex ischemia of the throat predisposes to the development of the antecedent and causative infection

Attempts have also been made particularly by investigators of previous generations to show that exposure to cold may have a more directly deleterious effect on the kidney There seem to be rather close interrelations between the cutaneous and renal circulations Cohnheim and Roy [99] Werthemer [100] and others found experimentally that chilling of the skin produces vasoconstriction followed by vasodilatation in the kidney i e the same reactions that occur in the skin Affanassiew [77] and others long ago found that chilling the skin of animals often results in renal lesions Similarly Johnson[101] noted that cold bathing is frequently followed by transitory proteinuria It would seem that large areas of the cutaneous surface must be chilled to result in proteinuria for Chodounsky Boucek and Polak[102] were unable to produce proteinuria by immersing their legs up to the knees for from ten to twenty minutes in water at a temperature of from 3 5° to 6 1° C Siegel[103] claimed to have produced parenchymatous nephritis in dogs by immersing their hind legs in water at 4° C for ten minutes, but his results were not confirmed by Polak [104] who did not observe even proteinuria if the dogs were prevented from assuming a lordotic position during the exposure Siegel and Gaisboeck[105] have pro-

duced severe renal changes in dogs and rabbits by exposing their kidneys and applying ice *directly to the surface*. However, the resulting lesions bore no close resemblance to those of human glomerulonephritis and of course the results of such coarse experiments can have no significance for the study of renal disease in man.

It does not seem to have been established that exposure of the body to cold produces a predisposition to renal disease through reflex ischemia of the kidneys or other effects on these organs.

Trauma.—The kidney is very sensitive to mechanical insults and proteinuria not uncommonly follows vigorous palpation, so-called renopalpatory albuminuria. Rayer[107] long ago described a traumatic nephritis, but as he apparently realized, his cases had nothing in common with any of the forms of Bright's disease. Since then numerous cases have been reported in which acute nephritis, sometimes with edema, has been attributed to trauma (Curschmann,[108] Koch,[109] and others). Orth[110] found inflammatory changes in the kidney of the rabbit after squeezing the side. In many of the cases reported, the onset of renal disease following trauma is doubtless a coincidence, and it must be left an open question whether trauma actually predisposes to glomerulonephritis.

BACTERIOLOGY OF ACUTE GLOMERULONEPHRITIS

The preponderant role of infection by streptococci in the etiology of acute glomerulonephritis is obvious from the diseases which it most commonly complicates—scarlet fever, sore throat, subacute bacterial endocarditis—the first of which is always due to streptococci and the last two almost invariably. Infected wounds and localized suppurations which are followed by true glomerulonephritis practically always contain streptococci either as the primary cause or as secondary invaders. Also the infectious purpuras, which are not uncommonly complicated by acute glomerulonephritis, are at least often due to streptococci. On rare occasions glomerulonephritis complicates rheumatic fever, which seems to be a manifestation of streptococcic infection. In acute glomerulonephritis following exposure to cold, streptococci have several times been demonstrated in the urine; in such cases an undetected streptococcic infection of the throat was probably present. For these reasons, beginning more than three decades ago, almost all students of the subject (*e. g.*, Longcope,[3] and coworkers, Winkenwerder, McLeod and Baker,[111] Marriott,[112] Clausen[3]) realized that streptococci are almost invariably the organisms responsible for acute glomerulonephritis. Further evidence of the role of streptococci in the causation of glomerulonephritis is afforded by Longcope's demonstration of increased skin reactivity to streptococcal filtrates and augmented antistreptolysin content of the blood (see below). The variegated and convincing supports for the predominantly streptococcic etiology of glomerulonephritis are summarized in the recent paper of Rammelkamp and Weaver.[113]

That different varieties of streptococci can cause glomerulonephritis is immediately shown by the fact that the disease complicates throat infections due to hemolytic streptococci and subacute bacterial endocarditis due

to Streptococcus viridans Longcope and his coworkers demonstrated Streptococcus hemolyticus in the infectious foci of 68 7 per cent and Streptococcus viridans in 12 7 per cent of their cases of glomerulonephritis Evidence has recently been adduced that among Group A hemolytic streptococci certain immunologic types are especially apt to produce glomerulonephritis Typing by the precipitin method of Lancefield Rammelkamp and Weaver[113] found that 26 of 31 attacks of acute glomerulonephritis were due to Type 12 Confirmation of these observations was obtained by Wertheim *et al* [114] who observed that 51 per cent of the type-specific hemolytic streptococci isolated from throat cultures in various stages of glomerulonephritis belonged to Type 12

While there is no doubt that streptococcic infections are responsible for the vast majority of instances of glomerulonephritis the nature of the connection is obscure Why for instance are some streptococcic infections followed by rheumatic fever and others by glomerulonephritis? It is rare for both to occur in the same patient but when the rheumatic cardiac later develops subacute bacterial endocarditis glomerulonephritis may complicate the picture Nor do we know why some very mild streptococcic infections are followed by glomerulonephritis while other severe infections with bacteremia and passage of many organisms through the kidney into the urine are not accompanied by renal lesions Thus in puerperal sepsis and erysipelas streptococci are often present in the urine, and may be found post mortem in the kidneys but glomerulonephritis is rare In the cases of tonsillar sepsis that I have seen glomerulonephritis has been absent while very mild tonsillitis may produce the disease Nor does adequate and seemingly successful treatment of streptococcic sore throat necessarily prevent the subsequent development of glomerulonephritis Rammelkamp and Weaver believe that the answer to some of these questions lies in the existence of strains of streptococci which are especially nephritogenic In support of this theory they adduce their finding that Type 12 streptococci are especially apt to produce glomerulonephritis the widely varying incidence of glomerulonephritis complicating scarlet fever in different years and the occurrance of epidemics of glomerulonephritis in family groups schools military installations etc I have also seen a very few instances of multiple occurrence of glomerulonephritis in a family (usually years apart) but they have been too few in number to be interpreted as more than coincidental However the possibility that certain types of streptococci are more apt than others to produce nephritis is plausible and worthy of further investigation The problem of the role of the host in the relation between the infectious focus and glomerulonephritis is considered below in the section on pathogenesis

In connection with the role of streptococcal infection in chronic glomerulonephritis an interesting point has been brought out by Seegal Seegal and Lyttle[88] They found that the admission rate for glomerulonephritis is about the same in hospitals in the South and in the North of the United States It has been established that the admission rate for rheumatic fever and scarlet fever—two diseases in which hemolytic streptococci are concerned and which present other analogies with glomerular nephritis—is much less in the southern hospitals The reason for this difference is ob

cure, and its elucidation might well add substantially to knowledge of the etiology of these diseases

The pneumococcus influenza bacillus gonococcus and meningococcus are also rare causes of glomerulonephritis *This is proven by* cases of subacute bacterial endocarditis or other chronic bacteremia due to these organisms with positive *blood cultures*, in which true glomerulonephritis develops during the infection

The *experimental* work of Long indicating the possibility that products of the tubercle bacillus may cause glomerulonephritis will be further discussed below

While it is very possible that other microorganisms are rare causes of infections leading to glomerulonephritis this has not been proved The fact that glomerulonephritis complicates on rare occasions such diseases as diphtheria measles chickenpox malaria and many others does not prove that the specific virus of each disease is responsible for the renal lesions, for these may be due to secondary infection with streptococci

PATHOLOGICAL ANATOMY OF ACUTE GLOMERULONEPHRITIS

In instances in which death has occurred during the first week of glomerulonephritis it may be impossible to discern any abnormalities in the kidneys with the naked eye and the existence of diffuse glomerular disease is discovered only in the sections In other early cases however as well as in practically all later ones the kidneys do present macroscopic alterations though these are often minimal and not always characteristic

The kidneys are of normal size or enlarged each weighing 200 grams or more Observations during decapsulation operations indicate that the kidneys are often larger during life than they appear at postmortem examination The consistency is generally softer than normal The *capsule strips readily* and without loss of substance revealing a surface which is pale-grayish brown or reddish brown in color Deeply congested kidneys which drip blood on section are sometimes *encountered where* venous stasis was present during life In early cases the color tends to be pale in later cases darker The stellate veins are often injected Tiny hemorrhagic points and streaks are usually but not always found

On section as a rule the cortex and medulla are well delimited from one *another the* medullary pyramids being deeply congested and much darker than the cortex In very early cases the kidney substance looks much as usual and the markings are fairly clear In later stages the kidney substance appears moist and clouded and the markings are indistinct at this time yellowish areas of fatty change may be present The glomeruli are sometimes more prominent than normally appearing either as pale translucent and grayish or else as dark red points in other instances they are hidden by the swollen parenchyma There may be jagged hemorrhagic streaks corresponding to tubules containing blood

Acute glomerulonephritis always involves both kidneys The cases of unilateral glomerulonephritis (Kolischer[115] and others) are based on urinary findings and are not supported by adequate anatomical evidence

Microscopic Picture.—Though many of the essential microscopic changes in acute glomerulonephritis were described by Klebs[1] the first adequate histological description was given by Langhans[2] in 1879. His observations were greatly amplified by Loehlein[3] and by investigations on very early cases of trench nephritis during World War I, notably by Dunn and MacNee[70] and Herxheimer. The study of McGregor[116] with the aid of special staining methods has clarified knowledge notably; in her paper and the subsequent one of Bell[117] from the same laboratory, will be found an exhaustive survey of the pathological histology of acute glomerulonephritis.

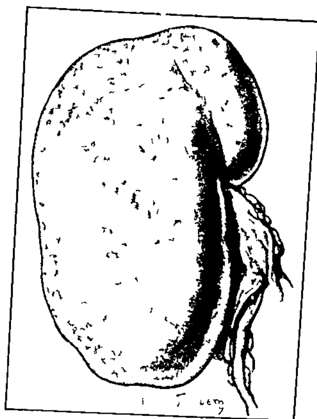


Fig. 24.—Acute glomerulonephritis. The kidney is swollen and its surface dotted with punctate hemorrhages.

The Glomeruli.—From the above and other researches, it is now known that *the first lesions involve the capillary loops of the glomeruli consisting in endocapillaritis.* During World War I, Herxheimer studied 13 cases of acute glomerulonephritis that died at very early stages of the disease, 5 in from one to three days after the first symptoms. He found the initial changes to consist in dilatation of the capillary loops which are mostly devoid of blood and filled with a coagulated protoplasmic exudate continuous with the capillary wall. The *extreme ischemia of the glomeruli* is also emphasized by Dunn and MacNee on the basis of 35 cases of trench nephritis. They found that in many kidneys of such cases not more than one or two loops in any section of a tuft contain red blood cells. The

ischemic loops are largely filled by cellular and other content which develops as follows

Very early in the process proliferation* of the endothelial cells of the capillary loops starts Normally the endothelial cells lining the glomerular capillaries are few in number and not easy to make out but in acute glomerulonephritis they swell so as to protrude into the lumen and proliferate Individual capillaries may be lined with several layers of such cells According to McGregor the appearance is as though many of the endothelial cells are actually desquamated into the capillary lumen Herxheimer's study of war nephritis indicates that in the very earliest phase of the dis-

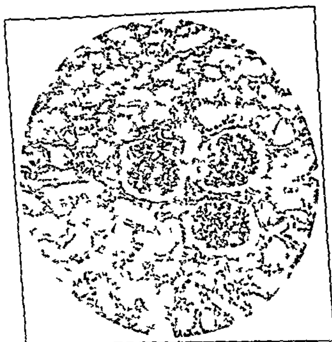


Fig 75 —Acute glomerulonephritis The *glomeruli* are almost completely ischemic due to blocking of the loops by swelling of the *endothelial* cells and cellular proliferation. The tubules are filled with albuminous fluid and there is blood *in some* (Same kidney as Fig 24)

case—which is so rarely seen at necropsy in civil life—the endothelial proliferation is not accompanied by multiplication of the glomerular epithelium But later proliferation of the epithelial cells outside the capillary basement membrane starts and becomes prominent McGregor found that the epithelial cells increase to two or three times the original number and swell in size so as to fill completely the space normally present between the lobules Accompanying the proliferation of the fixed elements is an

In ordinary necropsy *material* mitoses are very rarely demonstrable in glomeruli However by examining kidneys fixed thirty and forty five *minutes* after death Hartz et al[11] demonstrated *mitotic* divisions in the endothelial and *epithelial* cells in acute and subacute glomerulonephritis

Microscopic Picture —Though many of the essential microscopic changes in acute glomerulonephritis were described by Klebs,[1] the first adequate histological description was given by Langhans[2] in 1879 His observations were greatly amplified by Loehlein[3] and by investigations on very early cases of trench nephritis during World War I, notably by Dunn and MacNee [0] and Herxheimer [72] The study of McGregor[116] with the aid of special staining methods has clarified knowledge notably in her paper, and the subsequent one of Bell[117] from the same laboratory, will be found an exhaustive survey of the pathological histology of acute glomerulonephritis

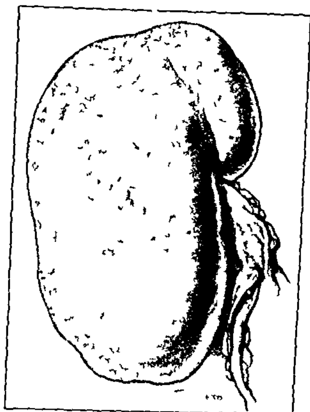


Fig 21 —Acute glomerulonephritis The kidney is swollen and its surface dotted with punctate hemorrhages

The Glomeruli —From the above and other researches, it is now known that *the first lesions involve the capillary loops of the glomeruli consisting in endocapillaritis* During World War I, Herxheimer studied 13 cases of acute glomerulonephritis that died at very early stages of the disease o in from one to three days after the first symptoms He found the initial changes to consist in dilatation of the capillary loops which are mostly devoid of blood and filled with a coagulated protoplasmic exudate continuous with the capillary wall The *extreme ischemia of the glomeruli* is also emphasized by Dunn and MacNee on the basis of 35 cases of trench nephritis They found that in many kidneys of such cases not more than one or two loops in any section of a tuft contain red blood cells The

The thickening leads to fusion of individual loops so that the appearance finally attained is often that of a syncytial network containing many nuclei McGregor has demonstrated by special stains that hyaline fibers appear in the lumens of the capillaries at a very early stage of the process She finds that these fibers are attached at one end to the glomerular basement membrane and form a network within the capillary loops Hyaline thrombosis may occur

These intracapillary and extracapillary changes lead to enlargement of the tuft so that it completely fills the capsular space and may protrude hernia like into the proximal convoluted tubule According to the measurements of Langhans the glomerulus may attain a diameter of 0 30 or 0 35 mm

In the very early cases of Herxheimer the epithelium of Bowman's capsule showed but slight swelling and fatty change Proliferation and desquamation occur only at a later stage But even in the earliest cases there may be hemorrhage into varying numbers of the capsular spaces which may also contain leukocytes coagulated protein and fibrin

While the glomerular epithelium may show no morphological evidences of damage in the earliest stages it has nevertheless been severely damaged This is shown by the presence of albuminous exudate and red cells in the capsular spaces as just mentioned Further evidence of damage to the epithelial cells of the glomerulus in the early stage was found by Langhans his description is translated here because of the importance of the findings for the pathogenesis of proteinuria in such cases If one examines the epithelium of a considerable number of glomeruli in the indicated way (i e by teasing) and also uses the same method on the glomeruli of inflamed kidneys the only abnormality found in the majority of the latter is that the epithelium cannot be obtained so easily in large shreds but rather in isolated elements which fall off on merely stroking the glomerulus with the needle The connection of the epithelial cells with one another has therefore become less through solution of the uniting cement substance perhaps also they are not so strongly attached to the capillary loops It is easy to see how protein can pass through the damaged capillaries and such a loosened epithelium into the capsular space resulting in proteinuria

Even in the earliest stages *almost all the glomeruli are involved* a fact which was already noted by Langhans and strongly emphasized by Loehlein Kuczynski[11] has communicated observations on renal complications of influenza which he believes to indicate that diffuse glomerulonephritis may start as a focal process but all other studies demonstrate that the disease is almost diffuse from the start (Dunn and MacNee Herxheimer Fahr and others) Here and there isolated glomerular loops may contain or even be congested with blood in the earliest stages but later the exudation and proliferation block the lumens of the capillary loops so that there results the practically complete ischemia of the tufts which is a characteristic feature of the process at its height In later stages permeable capillaries containing blood may indicate a healing phase It is probably from rupture of the few permeable and congested capillaries that hematuria results

accumulation of polymorphonuclear leukocytes within the glomerulus. This was studied by Graeff[19] by means of the oxydase reaction. He found that while in sections 15 microns thick the normal glomerulus contains from 3 to 25 leukocytes, in acute glomerulonephritis this number is increased and may even reach 100. In later stages, the number of leukocytes declines. The result of the cellular proliferation and accumulation is that the entire glomerular tuft is much more thickly beset with nuclei than normally (*Kernreichtum* of the Germans), which is often very striking on the first glance at the section under the low power.

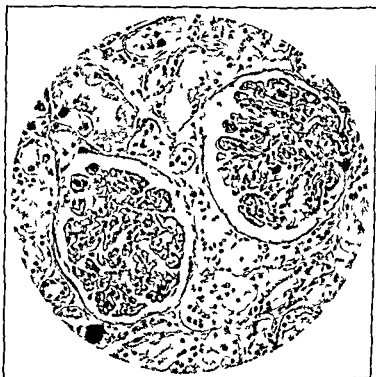


FIG 26 — Acute glomerulonephritis. Swelling of the capillary walls and ischemia of the loops.

In the foregoing, the increase in the number of nuclei in the glomerular tuft which characterizes the early stages of acute glomerulonephritis has been described as due to the proliferation of endothelial cells and accumulation of leukocytes within the capillary loops, *i.e.*, an intracapillary process. MacCallum championed the view that the nuclei in question arise from proliferation of connective tissue cells between the loops, *i.e.*, an intercapillary process. Jones[13] also believes that most of what has been regarded as endothelial proliferation in glomerulonephritis is actually migration of histiocytic cells into the interstitial spaces of the glomerulus. However, other evidence (see Bell) indicates strongly that the proliferation is actually initiated within the basement membrane of the capillary endothelium.

The normally delicate walls of the glomerular loops become thickened and appear hyaline or in other instances somewhat granular. Inasmuch as McGregor found little change in the basement membrane in the early stages, this change is probably largely due to swelling of the lining cells

of epithelial crescents makes its appearance. The tubular epithelium undergoes regressive changes. There is broadening of the interstices with accompanying interstitial infiltration. The appearance of these changes marks the transition to the subacute stage and will be discussed in detail in Chapter 21.

Little is known about the histological aspects of healing, for the obvious reason that such cases rarely come to necropsy. However a few instances in which death occurred from some complication during healing have been studied by Fahr[127] and others. The process of healing evidently starts with regression of the thickening of the walls of the loops and removal of the exudate which block the glomerular capillaries following which the previously ischemic capillaries become congested with blood. This explains the not uncommon observation that improvement in acute glomerulonephritis may be accompanied by an increase in the hematuria. That acute glomerulonephritis can heal without leaving any damage whatsoever is known from necropsies on individuals who have had the disease and die from some other cause years later without there being any evidence of the previous inflammatory process. In other instances, of course, healing is accompanied by obliteration of a greater or lesser number of glomeruli.

Summary.—Acute glomerulonephritis is a diffuse endocapillaritis of the glomerular loops. Its fundamental histological features are swelling and proliferation of the endothelial cells of the glomerular capillaries and accumulation of inflammatory exudate and leukocytes within the loops. Marked ischemia of the glomeruli results from the blocking of the glomerular capillaries thus produced. There is also proliferation of the glomerular epithelium, but this apparently starts subsequent to the endocapillary changes. Even in the earliest cases studied the process is very diffuse, sparing only isolated glomerular loops. Tubular lesions of consequence are not present in the earliest stages, only appearing later. In very severe cases there may develop in later stages inflammatory and necrotizing lesions of the vasa afferentia.

PATHOGENESIS OF ACUTE GLOMERULONEPHRITIS

How does a streptococcal infection of the lymphatic ring of the throat, often slight and apparently insignificant, result in acute glomerulonephritis? What is the mechanism of the connection between scarlet fever and the renal lesions that appear three weeks after the onset of the scarlatina, when the patient has often been afebrile for two weeks or more, and is seemingly completing his convalescence? Satisfactory answers to these questions cannot as yet be given, but much relevant data has been accumulated in recent years.

Direct bacterial invasion of the kidney from the primary focus *via the* blood stream is highly improbable. True glomerulonephritis is very rare in puerperal and other forms of sepsis—including tonsillar sepsis and early septic scarlet fever—despite the fact that the blood teems with [illegible] virulent streptococci or other bacteria and the urine may [illegible] numbers of the organisms. The forms of renal disease [illegible]

The Tubules and Interstices.—In the early stages the epithelial cells lining the tubules are little changed. There may be slight cloudy swelling or fatty change, but even this is sometimes absent. The tubules in the cortex are often dilated. In the lumen of the tubules are casts, erythrocytes, coagulated exudate, leukocytes, and exceptionally hemoglobin from laked red cells.

There are no interstitial changes in the early phases, apart from intertubular edema of varying degree and occasional leukocytic infiltrates around the glomeruli. The intertubular capillaries are usually dilated and filled with blood, in sharp contrast to the findings in the glomerular capillaries. Their walls moreover show no changes comparable to those in the glomerular capillaries, though occasionally the endothelial cells are somewhat swollen.

The Arteries.—In early cases the arteries appear normal in the usual examination of the sections. However, Kuczynski[122] has found by detailed study of serial sections that some, though not all, of the vasa afferentia exhibit such changes as edematous swelling, vacuolization and slight cellular infiltration of the wall close to the entrance into the glomerulus. These changes apparently are but slight. But in the later acute and early subacute stages of glomerulonephritis, there may appear severe inflammatory and necrotizing lesions of the arterioles which were first described by Loehlein[123] and have since been studied by Baehr and Sacks[124] and Jaffe.[125] I[126] found these lesions in 3 of 8 cases of later acute glomerulonephritis, in one of them the renal process was evidently less than three weeks old. The lesions consist essentially in a necrotizing arteriolitis of the vas afferens just previous to its entrance into the glomerulus, often accompanied by thrombotic occlusion of the lumen which may be projected into the first glomerular loops. I have seen small necroses of the glomerular capillaries accompanying the necrosis of the vasa afferentia. In some of Loehlein's cases the necrosis of the arteriolar walls was so severe that tiny aneurisms were formed with extravasation into the surrounding tissues. In all the cases in which I found necrotizing arteriolitis the renal process was very severe with death from renal insufficiency. It is to be emphasized that the necrotizing arteriolitis is not found in the earliest stages and when present involves only a fraction of the vasa afferentia; it cannot therefore be regarded as the cause of the glomerular lesions. Thrombosis of isolated arterioles is occasionally present.

It does not seem probable that the necrotizing arteriolitis of later acute and early subacute glomerulonephritis has any relation to the endarteritis and arteriolosclerosis found in the chronic stages of the disease (Chapter 21). The acute arteriolar lesions occur, so far as is known, in only very severe renal processes and it is unlikely that many such patients survive to go on to the chronic stage. The arteriolar lesions of chronic glomerulonephritis occur in many cases in which there is no history of a severe acute attack of the type in which necrotizing arteriolitis is present.

Chronicity and Healing.—If the patient does not improve and the renal process progresses after the first few weeks other changes appear. Thickening and hyalinization of the glomerular loops become more prominent and in some cases proliferation of the capsular epithelium with the formation

process of immunization A similar line of thought was followed by Longcope[131]

The following lines of evidence speak strongly in favor of this view that the processes of immunization with their accompanying hypersensitiveness are in some way as yet unclear connected with the development of glomerulonephritis following an infection

1 The fact has already been mentioned that glomerulonephritis complicating tonsillitis or scarlet fever develops not at the height of the infection but during convalescence when the symptoms of the primary disease are receding or have disappeared altogether

2 Clinical manifestations much akin to those of glomerulonephritis are not uncommon in serum sickness Thus Mackenzie and Hanger[132] state that Edema occurs in about one-third of all the cases (of serum disease), *and it has the distribution of nephritic edema* With the edema there is chloride and water retention a lowered phenolsulphonphthalein excretion diminished volume output albuminuria and cylindruria with rarely if ever a demonstrable nitrogen retention The impaired renal function is so far as we know always transitory ' Longcope and Rackemann[133] observed hypersensitive individuals in whom attacks of urticaria were accompanied by *characteristic manifestations of glomerulonephritis* In two instances the attacks of urticaria and erythema were accompanied by albuminuria cylindruria increase in blood urea profound depression of the index of urea excretion decrease in the output of phenolsulphonphthalein and retention of chlorides and water

3 Longcope[134] and his coworkers have studied the skin reactivity to filtrates of cultures of *hemolytic streptococci* recovered from tonsillar and sinus infections of individuals with glomerulonephritis They *found that* patients with glomerulonephritis give much more intense reactions than do controls including sufferers from tonsillitis

4 Friedemann and Deicher[135] found that the blood of patients with postscarlatinal *glomerulonephritis* contains far more antibodies than that of scarlatinal convalescents of the *same period* without glomerulonephritis But they did not find a high antibody content in the *serum of scarlatinal* patients with septic complications They therefore concluded that premature antibody formation in patients with postscarlatinal glomerulonephritis is a cause of the renal mischief Likewise Longcope[136] found that in cases of acute *glomerulonephritis* of abrupt onset following a severe throat infection or scarlet fever the titer of the *blood* in antistreptolysin (antibody against streptococcal hemolysin) rises to *high levels The same is true of rheumatic fever* another disease in *which there is good reason to suspect sensitization* to streptococci

Recently Lange[137] and his coworkers have found that the serum *complement* level is low in active glomerulonephritis Lange had previously found antibodies to human kidney in the *serum in glomerulonephritis* and attributes the low level of complement to a complement-binding antigen antibody reaction

5 Diffuse glomerulonephritis occurs much more *often in* [illegible] bacteria free and healed stages of *subacute bacterial endocarditis* [illegible] when the patient succumbs during *the stage of demonstrable* [illegible]

cases are abscesses, focal nephritis, acute interstitial nephritis or merely febrile proteinuria On the other hand numerous investigators have shown that the blood and urine are almost always sterile in patients with glomerulonephritis Wilson[69] found this to be the case in trench nephritis and Longcope[5] and his coworkers in various forms of glomerulonephritis in civil life Friedemann and Deicher[128] were unable to demonstrate microorganisms by culture of the urine of 11 patients in the acute stage of post scarlatinal glomerulonephritis, though 1 of the 11 urines did yield a pure culture of the scarlatinal streptococcus on intraperitoneal inoculation into mice It is true that streptococci have been found in some instances in the kidneys However, in the majority of cases of acute glomerulonephritis organisms cannot be demonstrated in the kidneys Thus, Bell and Hartzell[4] were able to find them in but 1 of 11 cases Those exceptional cases in which bacteria are found in the kidneys or urine do not indicate that the organisms found locally are necessarily the cause of the renal lesions for bacteria are often found in the kidneys of patients who had bacteremia without any glomerulonephritis whatsoever

These findings showed that the cause of glomerulonephritis is not the actual invasion of the kidneys by microorganisms The conception that next found favor was that *the renal process is the result of injury by a toxic substance* The diffuse nature of the glomerular injury also seemed to speak in favor of the toxic nature of the process

This conception of the toxic origin of glomerulonephritis appeared to be decidedly fortified by the discovery of the scarlatinal streptococcus with its powerful toxin by the Dicks and Dochez and the demonstration that the rash and other symptoms are due to the toxin Longcope and his coworkers also found that streptococci from infectious foci in patients with glomerulonephritis produce toxic filtrates which are often of considerable potency Trask and Blake[129] demonstrated the presence of the toxin of the scarlatinal streptococcus in the urine of 2 of 5 patients with scarlet fever On the basis of these and similar findings the conception arose that the streptococcic infections responsible for glomerulonephritis damage the kidneys through the intermediacy of toxins which injure the glomerular capillaries during excretion

But the pathogenesis of acute glomerulonephritis is doubtless more complicated than direct injury to the glomerular and other capillaries by the unaltered circulating toxic products of the microorganisms of the primary disease Such a conception would scarcely explain the remarkable fact that postscarlatinal glomerulonephritis appears during convalescence and not at the height of the disease when the fever rash and other symptoms demonstrate the presence of the scarlatinal toxemia A similar sequence of events occurs in glomerulonephritis of tonsillar origin Formerly it was thought that desquamation following scarlet fever affords an opportunity for injury to the kidneys as a result of chilling of the skin but there is no evidence in favor of this view Following the first studies on serum sickness and other allergic phenomena Schick[130] pointed out the analogy of the course of events in these conditions with the latent period between scarlet fever and postscarlatinal glomerulonephritis and suggested that *the renal complication depends on the development of a hypersensitive state in the*

nephritis' in rabbits by the injection of an autolysate of Type I pneumococcus and also by intradermal infection with virulent strains of pneumococci In some instances the renal lesions were associated with edema and ascites The occurrence of edema would indicate that the experimental simulation of human glomerulonephritis had been accomplished However, the few microphotographs reproduced by the investigators do not seem to me characteristic of the histological picture of glomerulonephritis Further details of these experiments would seem highly desirable

(b) Duval and Hibbard[12] were unable to produce glomerulonephritis in the *unimmunized* rabbit by the injection of living scarlatinal streptococci or filtrates of their cultures On the other hand they did succeed in producing glomerular lesions when the living cultures were injected into *immunized* rabbits And if they liberated the endotoxic substance of the streptococci by bacteriolysis in the peritoneal cavity of an immunized rabbit or by treating the cultures *in vitro* with activated homologous immune serum the filtrate also produced glomerular changes An attractive hypothesis—as yet unproved—would be that similar liberation of endotoxins occurs with the establishment of immunity in scarlet fever and results in glomerulonephritis and the other manifestations of the "second sickness" (arthritis adenitis etc) Duval and Hibbard designate the lesions they produced as glomerulonephritis but whether they are identical with the lesions in the human disease requires further study It is further worthy of note that Duval and Hibbard found that when they induced a general infection of the animal with scarlatinal streptococci the renal lesion was acute interstitial nephritis and not a glomerular change These findings agree very well with clinical observations for acute interstitial nephritis occurs in septic cases of scarlet fever with hematogenous dissemination of streptococci while glomerulonephritis appears during convalescence when there is no evidence of a general infection

(c) Long and Finner[13] found that the injection of tuberculin into the renal artery of non tuberculous swine did not produce glomerular lesions But if the animals was previously sensitized by a mild tuberculous infection the same procedure was followed by glomerular changes Here again further study is required to demonstrate if the lesions are entirely identical with human diffuse glomerulonephritis

(d) A very interesting experiment has been reported by Bell and Clawson[14] Over a period of four years they injected suspensions of a culture of Streptococcus viridans into the veins of a monkey The animal developed persistent proteinuria and frequent hematuria but no edema or hypertension death was apparently due to uremia At necropsy Bell and Clawson found a form of chronic diffuse glomerulonephritis characterized histologically by marked increase in the capillary endothelium and increase in the thickness and number of layers of the capillary basement membrane These findings indicate that Bell and Clawson produced a renal lesion at least closely simulating if not identical with human glomerulonephritis Furthermore the long duration of the experiment lends strong support to the theory that sensitization plays an important part in the pathogenesis of glomerulonephritis

One-third of Libman's[7] bacteria free and healed cases died of uremia, while the proportion of "active" cases that have this termination is exceedingly small. This theoretically and practically important fact has been established by the extensive studies of Libman and Baehr cited on p 533. The entrance of a patient with subacute bacterial endocarditis into the bacteria free or healed stages is, of course, evidence that the processes of immunization are active and have met with some success.

It was mentioned above that glomerulonephritis may develop in long standing bacteremia due to the gonococcus, pneumococcus, meningococcus or influenza bacillus. I have the impression from my own experience and from the literature that glomerulonephritis is less rare in such protracted infections than in acute infections due to the same organism, but I am unable to cite sufficient material to advance this statement as more than an impression except in the case of the gonococcus. In prolonged gonococcal bacteremia the development of glomerulonephritis seems to be the rule and not the exception.*

Perhaps in analogy to the considerable incidence in subacute bacterial endocarditis Lillehei[138] and his associates have observed glomerulonephritis in one third of dogs in which arteriovenous fistulas had been created six weeks to five months before. They have been able to produce glomerulonephritis and endocarditis in dogs with such fistulas by the injection of relatively small numbers of Beta Hemolytic Streptococci or Streptococcus Viridans. How the cardiovascular stress due to the arteriovenous fistula abets the bacteremia in the production of the glomerulonephritis and endocarditis remains to be determined.

6. A number of attempts have been made to produce glomerulonephritis experimentally in sensitized animals.

(a) The first work along this line was that of Longcope.[131] He was able to produce renal lesions in dogs, rabbits and other animals by repeated injections of horse serum and egg white, among which were marked glomerular changes.

Subsequently this line of investigation was pursued in detail by Longcope[139] and his pupils. By the injection of suspensions of heat-killed hemolytic streptococci into the renal artery of rabbits, Lukens and Longcope were able to produce glomerular lesions in about one-half the animals used. The glomerular lesions were much more frequent in rabbits in which an acute localized infection had previously been induced by the intracutaneous injection of living streptococci than in normal animals. The occurrence of acute glomerulitis was generally associated with a well marked skin reaction to filtrates of hemolytic streptococci. The glomerular lesions were apparently not diffuse and, as pointed out by Lukens and Longcope, are not to be considered as strictly analogous to human glomerulonephritis. McLeod and Finney[140] produced similar lesions by the injection of suspensions of Streptococcus viridans into the renal artery. Further experiments have been reported by Blackman, Brown and Rake.[141] They produced what they term "characteristic acute and subacute

* Dr George Baehr informs me that he found glomerulonephritis in 5 of the last 6 cases of gonorrheal endocarditis that came to necropsy at Mount Sinai Hospital (before the days of penicillin).

toxin.* They were able to prevent renal damage by preceding the injection of this serum by an intravenous injection of saline extract of *rat kidney*. Presumably the rat kidney extract combines with the anti-rat kidney serum and thereby prevents the nephrotoxic action of the latter. In interesting analogy with the interval between the causative infection and the development of glomerulonephritis in man, experimental nephrotoxic nephritis appears only after a latent period following the injection. Sarre[161] found that if one renal artery is obstructed for fifteen minutes after the injection of nephrotoxic serum, nephritis develops only in the other kidney. Kay[162] has endeavored to elucidate these findings by experiments with glomerulonephritis produced in the rabbit with anti-rabbit kidney duck serum. His observations indicate that the specific antibodies for the rabbit kidney in the duck serum combine immediately after injection with the kidney of the injected rabbit. The rabbit then produces antibodies for the normal proteins of the injected duck serum, which interact with the combination of the injected duck antibody-rabbit kidney combination now functioning as an antigen. This secondary interaction results in nephritis, which therefore does not appear until the rabbit has had time to form antibodies to duck proteins. Kay's findings accord with the hypothesis that human glomerulonephritis results from the interaction of antibodies with an antigen formed by the action of some product of streptococcic infection on the kidney.

But the significance of the experiments for the pathogenesis of the human disease remains to be determined. In any event the demonstration that antibodies can be produced which damage the kidney in a fashion that is at least closely related to glomerulonephritis is at least in excellent harmony with the conception that sensitization to bacterial infection and the mechanisms concerned in the development of resistance to infection are in some obscure way concerned in the pathogenesis of human glomerulonephritis.

Parenthetically, it may be mentioned that Hepler and Simonds[163], working along the line of the Arthus phenomenon, have produced anaphylactic inflammation in the kidneys of rabbits. They sensitized rabbits by repeated subcutaneous injections of a protein and then injected the protein directly into the kidney. A severe hemorrhagic and necrotizing inflammation resulted, but the description reveals no morphological analogies to glomerulonephritis.

(*f*) *Production of Glomerulonephritis by Autoantibodies*.—Cavelti and Cavelti[165] found that treatment of an emulsion of rat kidney with killed group A streptococci renders the kidney material antigenic in the same species. By immunization of rats with such a mixture they produced antibodies to rat kidney and glomerulonephritis. They bring evidence that

* Not only are these nephrotoxic antibodies relatively organ specific for the kidney, but Pressman et al. found by labeling with radioiodine that they localize primarily in the glomeruli. Similarly Solomon[166] and his associates showed that the nephrotoxins of anti-rat kidney sera can be removed by adsorption with suspensions of glomeruli but not by suspensions of tubules or other tissues. But despite the specific fixation of these antibodies in the glomeruli they apparently can be evoked by antigens other than the kidney. Seegal and Loeb found that glomerulonephritis indistinguishable from that obtained with rabbit anti-rat kidney serum can be produced by injections of rabbit anti-rat placenta serum.

(e) *Production of Glomerulonephritis with Anti-kidney Serum*.—By the injection of anti kidney serum, Masugi[145] produced a very close simulation of human glomerulonephritis. His results have been confirmed and extended by Smadel, *et al.*,[146] Arnott *et al.*[147] and others. Masugi found that if a rabbit is repeatedly injected with a suspension of rat's kidney, subsequent injection of the rabbit's serum into a rat produces a clinical and anatomical picture closely resembling that of human glomerulonephritis. Arnott and his associates prepared their anti-kidney serum by injecting a suspension of rabbit kidney into a duck. By injecting hens with dog kidney, Fouts[148] *et al.* prepared an anti-dog kidney nephrotoxic serum which produced renal changes in the dog similar to those produced by nephrotoxic sera in the rat and rabbit.

The clinical picture produced by the injection of the anti kidney serum is characterized by proteinuria, cylindruria, renal insufficiency with azotemia, hypoproteinemia, lipemia, and hypertension. While hematuria often occurs, Smadel found that it is part of an anaphylactoid reaction and is not due to the specific nephrotoxin. Smadel and Farr produced rapidly fatal nephritis by injecting relatively large amounts of antikidney serum at frequent intervals and a chronic type of duration of even a year by giving small quantities in single or repeated dosage. Farr and Smadel made interesting observations regarding the relation of the diet to the course of experimental nephritis. They found that 13 of 15 rats which were given a low-protein diet after a single injection of anti kidney serum had recovered within eight and a half months. On the other hand 8 of 15 similarly injected rats which were given a high protein diet died of renal failure within five and a half months and 6 of the remainder were definitely abnormal.

Anatomically the injection of the anti kidney serum is followed by changes in the glomeruli and tubules. The basement membrane of the glomerular loops becomes thickened and there may be swelling of the endothelial cells. The degree of proliferation of the endothelial nuclei varied in different observations. There is proliferation of the capsular epithelium with the formation of crescents. With longer duration of the process connective tissue proliferation converts the glomerulus into a scar. Thrombosis of glomerular loops may occur but is attributed by Smadel to an anaphylactoid reaction not due to nephrotoxin alone. The tubules undergo various regressive changes which may attain necrosis; there are areas of tubular dilation and the formation of casts. Interstitial fibrosis develops. When the lesion is present for a long time Smadel describes widespread vascular lesions (arteriolar thickening, hyalinization, fatty change, fraying of the internal elastic membrane, calcification) with areas of secondary degeneration in various organs. Cardiac hypertrophy may develop in such instances.

It is evident that these investigators have produced a remarkable simulation of human glomerulonephritis. But the mechanism of nephrotoxic nephritis is not simple and by no means completely understood. Swift and Smadel showed that the effect of the anti kidney serum on the kidney is dependent on a relatively organ specific antibody called nephro-

toxin * They were able to prevent renal damage by preceding the injection of this serum by an intravenous injection of saline extract of rat kidney Presumably the rat kidney extract combines with the anti rat kidney serum and thereby prevents the nephrotoxic action of the latter In interesting analogy with the interval between the causative infection and the development of glomerulonephritis in man experimental nephrotoxic nephritis appears only after a latent period following the injection Sarre[illegible] found that if one renal artery is obstructed for fifteen minutes after the injection of nephrotoxic serum nephritis develops only in the other kidney Kay[illegible] has endeavored to elucidate these findings by experiments with glomerulonephritis produced in the rabbit with anti rabbit kidney duck serum His observations indicate that the specific antibodies for the rabbit kidney in the duck serum combine immediately after injection with the kidney of the injected rabbit The rabbit then produces antibodies for the normal proteins of the injected duck serum which interact with the combination of the injected duck antibody rabbit kidney combination now functioning as an antigen This secondary interaction results in nephritis, which therefore does not appear until the rabbit has had time to form antibodies to duck proteins Kay s findings accord with the hypothesis that human glomerulonephritis results from the interaction of antibodies with an antigen formed by the action of some product of streptococcic infection on the kidney

But the significance of the experiments for the pathogenesis of the human disease remains to be determined In any event the demonstration that antibodies can be produced which damage the kidney in a fashion that is at least closely related to glomerulonephritis is at least in excellent harmony with the conception that sensitization to bacterial infection and the mechanisms concerned in the development of resistance to infection are in some obscure way concerned in the pathogenesis of human glomerulonephritis

Parenthetically it may be mentioned that Hepler and Simonds[illegible] working along the line of the Arthus phenomenon have produced anaphylactic inflammation in the kidneys of rabbits They sensitized rabbits by repeated subcutaneous injections of a protein and then injected the protein directly into the kidney A severe hemorrhagic and necrotizing inflammation resulted but the description reveals no morphological analogies to glomerulonephritis

(f) *Production of Glomerulonephritis by Autoantibodies* —Cavelti and Cavelti[135] found that treatment of an emulsion of rat kidney with killed group A streptococci renders the kidney material antigenic in the same species By immunization of rats with such a mixture they produced antibodies to rat kidney and glomerulonephritis They bring evidence that

* Not only are these nephrotoxic antibodies relatively organ specific for the kidney but Pressman *et al* [illegible] found by labeling with radioiodine that they localize primarily in the glomeruli Similarly Solomon[illegible] and his associates showed that the nephrotoxins of anti rat kidney sera can be removed by adsorption with suspensions of glomeruli but not by suspensions of tubules or other tissues But despite the specific fixation of these antibodies in the glomeruli they apparently can be evoked by antigens other than the kidney Seegal and Loeb[illegible] found that glomerulonephritis indistinguishable from that obtained with rabbit anti rat kidney serum can be produced by injections of rabbit anti rat placenta serum.

the renal lesions are due to the action of the antibodies on the kidney. If action of products of human streptococcic infection on kidney were similarly demonstrated to evoke antibodies to kidney, a very appealing explanation of the pathogenesis of glomerulonephritis as due to effects of these antibodies on the kidney would be presented. However Humphrey[156] was unable to reproduce Cavelti's results.

(g) *Globulin Glomerulonephritis.*—Recent experiments indicate that glomerulonephritis can be induced by injection of serum globulins. Haun and Janeway[157] accomplished this in rabbits by a single injection of purified bovine serum gamma globulin; the lesions were most marked a week after injection. More and Waugh[158] produced a high incidence of glomerulonephritis in unilaterally nephrectomized rabbits by two successive doses of purified serum gamma globulin. The lesions were closely similar to human acute and subacute glomerulonephritis. McClean[159] and his associates caused glomerulonephritis in rabbits by daily intravenous injections for three to thirteen months of small amounts of horse serum. The renal lesions went on to the chronic stage with scarring and atrophy and azotemia.

Inasmuch as a high proportion of antibodies seem to be included in the gamma globulin fraction, the pathogenetic mechanisms of experimental nephritis produced by anti-kidney serums and by the injection of gamma globulins may not be dissimilar. And the possible analogy of these forms of experimental renal disease to human glomerulonephritis, which so characteristically develops with the immune response to an infection, seems highly plausible.

These various lines of evidence point strongly to the participation of allergic factors in the pathogenesis of glomerulonephritis. But the actual mechanism by which the allergic response to a streptococcic infection participates in the production of glomerulonephritis still remains an open field for investigation.

Acute Glomerulonephritis as a General Capillary Disease.—In recent years the view has steadily gained ground that acute glomerulonephritis consists not merely in an affection of the glomerular capillaries but that the glomerular lesions are but one manifestation of a general injury to the capillaries of wide areas of the body. This is really an old theory, for Cohnheim and Lichtheim[160] long ago adduced evidence that edema in postscarlatinal glomerulonephritis is the result of injury to the cutaneous capillaries. Strongly in favor of the theory of acute glomerulonephritis as a general capillary disease is the fact that edema sets in very early in the disease, often almost simultaneously with the proteinuria. Indeed some cases have been described in which edema preceded proteinuria and even such in which the edema and hypertension were not accompanied by proteinuria at all (see Chapter 20). We have seen in the chapter on Edema that some observations of high protein content of the anasarca fluid in acute glomerulonephritis indicate the presence of injury of the subcutaneous capillaries with resultant increase in permeability. These observations, however, have been disputed (p. 150).

The direct microscopic studies of the capillaries of the nail bed in acute glomerulonephritis by Weiss,[161] Boas,[162] Hahn,[163] Marriott[11] and others have

led to conflicting results Weiss found the capillaries to be unusually thick and tortuous and the blood flow slowed Hahn observed the flow to be alternately slowed and accelerated Marriott described the capillaries in glomerulonephritis as tortuous with spastic contraction of the arterial limb and distention of the venous limb Boas and Kylin[164] are not inclined to attribute significance to these findings for they believe that similar variations are encountered under physiological condition But the work published seems to have established that capillary constriction is present in at least a considerable proportion of the cases Kylin claims that the capillary pressure is increased in acute glomerulonephritis However the methods for estimating capillary pressure are not satisfactory and Kylin's results have not been confirmed by Boas and Klingmueller[164] The absence of characteristic histological changes in the capillaries in edematous areas has already been mentioned The occasional occurrence of petechiae and the often positive tourniquet test in acute glomerulonephritis are perhaps manifestations of capillary injury

The occurrence of edema in acute glomerulonephritis at the very start of the disease when the plasma albumin concentration is normal and there is no heart failure renders the theory of generalized capillary damage very attractive But the theory needs more support before it can be accepted it was seen on p 150 that observations on the protein content of the edema fluid have yielded discordant results And even if the existence of widespread capillary injury in acute glomerulonephritis should be substantiated one encounters the further difficulty of explaining why the glomerular capillaries are so much more severely damaged than the others It seems probable that the severe injury to the glomerular capillaries is in some way connected with their excretory function for even the neighboring inter tubular capillaries show as little morphological evidence of damage as those in other organs

Volhard's Hypothesis of the Angiospastic Origin of Acute Glomerulonephritis — Volhard[166] proposed an ingenious and novel explanation of the pathogenesis of acute glomerulonephritis One of the striking features of the histological picture of acute glomerulonephritis is the small number of red blood cells in the glomerular capillaries often verging on total ischemia Volhard noted that the vasa afferentia are likewise devoid of red cells though they are often dilated He reasons that if the cause of the glomerular ischemia is blocking of the capillaries by swelling of the walls and inflammatory exudate the vasa afferentia should contain blood In view of the absence of blood from these vessels he believes that the glomerular ischemia is due to a block of the circulation before the terminal portions of the vasa afferentia Not finding organic lesions of these vessels in the early stages he holds that the circulatory obstruction is functional consisting in a spasm of the smaller arteries Volhard regards the glomerular lesions as an expression of the reaction to the resulting ischemia Volhard believes that the arteriolar spasm is not confined to the kidney but is universal and thereby accounts for the hypertension the retinal lesions when present and the pallor of the skin He even accounts for the edema by ischemic injury to the capillaries In favor of this angiospastic theory of acute glomerulonephritis Volhard and his pupils have adduced the following evidence

1 Huelse[167] found that the glomeruli of kidneys of patients who succumbed to acute glomerulonephritis can be injected with citrated blood or India ink despite the fact that control sections show them to be completely ischemic Volhard and

Huel e believe that this finding demonstrates that the glomerular ischemia is due to arteriolar spasm which is of course, relaxed after death and permits the injection of the glomerular capillaries

2 Huelse and Strau s[163] claim to have demonstrated in the blood of patients with glomerulonephritis and eclampsia gravidarum a substance which sensitizes the arterioles to epinephrine and thereby results in the arteriolar spasm They originally believed the sensitizing substance to be peptone like, but then found this improbable for blood filtrates which they tested gave no biuret reaction

3 Koch[168] found that the rise in blood pressure may precede the urinary changes of postscarlatinal glomerulonephritis

Volhard s hypothesis of primary vascular spasm in acute glomerulonephritis has met with little support apart from an elaborate anatomical investigation by Kuczynski,[1 2] whose findings do not appear unequivocal and are largely controverted by Hueckel [169] who studied a case that succumbed only thirty hours after the onset On the other hand, there has been much opposition Fahr[1 0] points out that in the very earliest cases some of the capillary loops may contain blood The vas afferens is by no means always devoid of blood in a case investigated in serial sections by Fahr, many of the vasa afferentia contained large numbers of red cells I have several times made the same observation, as have others Moreover, the capillary loops are not empty but as has been described on page 549, their lumens are narrowed or obliterated by swelling and proliferation of the endothelial cells and other inflammatory exudation The claim of Huelse and Strauss that an epinephrine sensitizing substance is present in the blood in acute glomerulo nephritis has never been confirmed and would not prove that the vasoconstriction is the primary factor And Huelse s finding that the glomeruli in acute glomerulo nephritis can be readily injected, is contrary to the old observations of Langhans and others that the glomeruli in this condition can be injected only under a higher pressure than is normally required and then but incompletely Hayman[1 1] has al o found that the resistance to perfusion of the kidney is increased in acute glomerulo nephritis Finally hypertension only exceptionally precedes urinary abnormalities in postscarlatinal glomerulonephritis It is thus seen that none of the findings on which the angiospastic hypothesis of acute glomerulonephritis is based is un equivocal and it cannot be accepted as even probable

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Chapter

20

ACUTE GLOMERULONEPHRITIS II CLINICAL PICTURE, DIAGNOSIS, PROGNOSIS, AND TREATMENT

CLINICAL PICTURE OF ACUTE GLOMERULONEPHRITIS

The clinical picture of acute glomerulonephritis is peculiarly variegated due not only to the predominance of one or another symptom of the glomerulonephritis itself but also to the frequent concomitance of other manifestations of the causative infection In the one instance the evidence of the disease consists in little more than urinary abnormalities revealed by routine examination of the urine after scarlet fever or another infectious disease while in other cases there is an extremely severe clinical picture with marked edema, cardiovascular manifestations and uremia The disease may run its course in a few days or far more commonly in some weeks, while in other instances it lasts for months or enters a chronic phase and there are unusual fulminant cases which terminate fatally within a few days or weeks

Onset —The onset may be acute or insidious The following are some of the many ways in which acute glomerulonephritis is first manifested

1 A *latent* period may constitute the first phase of the disease during this time there are no subjective symptoms and the renal mischief is discovered only as a result of routine urinary examination following an infection

2 *Edema* is very often the initial symptom Following sore throat or another infectious disease quickly after exposure to cold or wet or without any ascertainable cause the patient notices in the morning that his eye-lids are puffy or it may be pointed out to him by others Less commonly swelling of the feet or genitalia is the first sign

3 *Urinary symptoms* may be noticed first There is bloody and scanty urine Occasionally there are also frequency urgency and pains in the lumbar region radiating downward thus simulating disease of the urinary passages

4 In other instances particularly following severe sore throat or exposure to cold and wet the disease sets in with violent *symptoms of an acute infection* such as high fever chills headache and bodily pains particularly in the back Vomiting is a common initial manifestation in children Edema then appears, or in unusual cases it may not come on at all, so that the diagnosis is first suspected from the urinary examination

5 There are cases particularly in children which start with *cerebral symptoms* such as headache convulsions transitory palsies and vomiting

I saw two such cases within a short time which were at first considered as epidemic encephalitis

6 In war nephritis dyspnea was a common initial manifestation, having been present in 34 of Dunn and MacNee's[1] cases But it is rarely among the chief initial complaints in glomerulonephritis as seen in civil practice

7 In children less often in adult the onset may be *insidious* with weakness pallor loss of appetite thirst and perhaps slight edema, the cause of which is cleared up only on examination of the urine

Acute glomerulonephritis is undoubtedly very often not detected This is revealed by cases of chronic glomerulonephritis in which no history of the acute stage can be obtained

General Course of Acute Glomerulonephritis —In the following some of the more common variants of the clinical course of the disease will be sketched and then the individual symptoms considered in more detail

In many instances as mentioned above acute glomerulonephritis is manifested by *little more than urinary abnormalities* Following sore throat scarlet fever or another infection examination of the urine reveals protein blood and casts Careful observation particularly by one who has seen the patient previously may detect a slightly puffy appearance of the face Or there may be transitory elevation of the blood pressure to some such level as 135/90 mm which is seen later to be above the normal for the individual The slight extrarenal manifestations if present at all quickly disappear and then the urinary abnormalities clear up most often in the course of weeks but sometimes in a few days The patient either feels comparatively well or else complains of weakness lassitude anorexia etc symptoms which may quite as well be after-effects of the primary infection as manifestations of the glomerulonephritis Such cases represent the mildest form of acute glomerulonephritis and are detected only when the urine is carefully studied during and after infections Most such cases following tonsillitis and probably very many after scarlet fever are overlooked in the general routine of practice They may not even have come to the physician for the original sore throat In all likelihood such mild attacks initiate the many instances of chronic glomerulonephritis in which no history of the acute phase of the disease can be obtained

Another group of cases is that in which the clinical picture is dominated by *edema* Renal function is not seriously impaired hypertension is slight or even if well marked does not cause cardiac failure and cerebral manifestations are absent The edema may disappear within a few days though more often it lasts longer and may wax and wane for months as the disease enters the chronic phase

In other instances particularly in children the urinary findings edema and hypertension are thrown into the background by the appearance of convulsions or other manifestations of *hypertensive encephalopathy* There may be but one such seizure or they may follow close on one another as in status epilepticus and then constitute a grave immediate danger to life If the patient survives the convulsive seizure the disease usually pursues its previous course though in some instances marked amelioration of symptoms follows I recently saw a middle-aged woman with old

essential hypertension in whom sudden headache, vertigo vomiting and disorientation led to diagnosis of cerebral hemorrhage or thrombosis, actually, there was acute glomerulonephritis

A further clinical type of acute glomerulonephritis is constituted by the cases in which *arterial hypertension* and heart failure are the most prominent features, as a rule accompanied by edema, less often by almost none Cases of this type occur particularly in adults There are marked dyspnea and other evidence of myocardial insufficiency, sudden failure of the left ventricle with resultant pulmonary edema may occur This is an unusual form of the disease, and is the one most likely to lead, in adults, to death in the acute stage

Above were mentioned the cases that start with high fever chills and other *manifestations of a severe general infection* This picture usually quickly subsides—though in rare instances death may occur at this time—and the disease then runs the usual afebrile course of glomerulonephritis These severe general symptoms are probably due to the general infection rather than to the glomerulonephritis and in the rare cases in which the fever stays high for more than a few days, another infectious focus or bacteremia can generally be demonstrated

At any period of the clinical course, but particularly at the start, the oliguria which is an almost constant feature of the disease may become intensified so that the patient passes extremely little urine or rarely becomes totally anuric Under these circumstances, retention of urinary constituents occurs and the picture soon becomes that of *uremia* with its characteristic nervous and gastro-intestinal manifestations and its grave outlook On rare occasions anuria may alone usher in the disease as in the following interesting case

An elderly male was admitted to the Surgical Service of Dr Edwin Beer at Mount Sinai Hospital his sole complaint being that he had not urinated at all for a week Otherwise he felt well There was marked nitrogen retention but no hypertension or edema Inasmuch as anuria persisted, decapsulation was carried out two days after admission and a small piece of kidney removed which revealed acute glomerulonephritis The anuria continued and death from uremia occurred on the fourteenth day the diagnosis of acute glomerulonephritis was verified at necropsy From beginning to end the only symptoms were anuria and, in the last days the consequent uremic manifestations However it should be borne in mind that sudden onset of extreme oliguria or anuria is more apt to result from necrotizing nephrosis (lower nephron nephrosis) than from acute glomerulonephritis

Finally there are unusual very severe cases characterized by copious *hematuria and rapidly progressive renal insufficiency* from the very start with little edema and no hypertension Most of the cases of this variety that I have seen died in the acute stage

The Individual Symptoms —EDEMA —Dropsical swelling of the skin is to the laity *the* sign of the disease It is present in the large majority of patients with glomerulonephritis but may be absent in the very mild cases and also on rare occasions in the most severe It usually appears very early, but may supervene only after the urinary abnormalities have been present for some time The edema may come on suddenly and rapidly

attain a high degree or its appearance may be gradual so that for some time the only manifestation is a bloated appearance of the face recognizable as abnormal only to those who have previously known the patient In young children in hospitals the onset of edema is sometimes first detected by the scale a stage of so-called pre-edema preceding demonstrable swelling The sudden onset of edema without a protracted stage of pre-edema can be observed in children whose weight has been followed after sore throat or scarlet fever

The localization is variable Most characteristic of nephritic edema are those cases in which the edema first affects the face appearing as a swelling of the loose cellular tissue of the eyelids and imparting a bloated appearance to the face Such swelling of the face combined with a whitish pallor constitutes the characteristic nephritic facies which often enables the diagnosis of renal disease at a glance Very often the swelling of the face is noted in the morning to diminish during the day In other cases the first swelling is found around the ankles and sometimes it starts in the loose cellular tissue of the scrotum or vulva In patients who have been in bed for their primary disease the first edema may be over the sacrum In still other instances various parts are affected simultaneously

In many cases the edema is confined to the initial localization but in others it increases rapidly in degree and extent However since the introduction of salt restriction extreme general anasarca is rarely seen in acute glomerulonephritis Nowadays since salt restriction has become almost universal and treatment with large volumes of milk has been abandoned the edema of acute glomerulonephritis is usually but modest in degree The subcutaneous edema may be accompanied by effusions into the serous cavities most often the peritoneum and pleura which may be so extensive as to demand paracentesis Further details as to the distribution of the edema and the symptoms due to it will be found on page 144 Here we may call attention to the very rare but extremely dangerous complication of edema of the larynx which may rapidly cause death by suffocation It is sometimes preceded by edema of the fauces and may occur either as part of generalized edema or alone (Dieulafoy[2]) Since salt restriction has come into use laryngeal edema is no longer seen in adults Attention has been called to the fact that pulmonary edema is more often due to cardiac failure than directly to the general edematous tendency, and that cerebral edema is probably due to circulatory disturbances in the brain consequent on the hypertension (p 304) The most extreme general anasarca may be present without any pulmonary or cerebral edema

The relation of the edema to the other phenomena of the disease is very variable In some mild cases it is entirely absent It may be very transitory or persist obstinately over months as the disease enters the subacute phase In other instances the edema disappears despite the fact that the persistence of the hypertension and urinary changes reveal that the disease is still present In some of the most severe cases there is no edema at any time In several cases of this variety that I have seen in addition to the ordinary lesions of acute or subacute glomerulonephritis there were necroses of the vasa afferentia and some in the glomeruli In these cases the toxic agent apparently acts almost entirely on the kidney not damaging

the extrarenal capillaries sufficiently to produce edema In other instances of severe glomerulonephritis, the absence of edema is doubtless due to the fact that the patients ingest no salt and/or vomit

The edema fluid during the acute stage of glomerulonephritis is clear and not opalescent as is so often seen in the nephrotic edema of the later stages of the disease and of chronic nephrosis The subcutaneous edema is rarely sufficiently abundant to enable one to obtain an uncontaminated specimen for examination The pathogenesis and protein content of the edema are discussed on p 150

In addition to the renal variety, edema of cardiac origin may occur in acute glomerulonephritis, it is to be recognized by the coexistence of other symptoms and signs of cardiac insufficiency

Arterial Hypertension —The classical picture of acute glomerulonephritis includes arterial hypertension But it is more often absent or at least not definitely demonstrable than is edema Like the latter, it is frequently absent or only transitory in mild cases In tuberculous and other cachectic patients hypertension is mostly, though not always, slight or absent In children, hypertension is more apt to be absent than in adults In the exceptional cases of acute glomerulonephritis in the forties or fifties hypertension is much more apt to be severe and prolonged than in younger patients Cardiac failure may at any time reduce the hypertension

The rise usually affects both the systolic and diastolic pressures However, the elevation in either may be the more prominent It is perhaps, more frequent for the diastolic rise to be proportionately greater But it is important to bear in mind that there are cases particularly in children in which only the systolic pressure is elevated this is most common at the onset As a rule the hypertension is moderate in degree the most common systolic pressures in adults being between 130 and 170 mm Pressures exceeding 200 mm systolic and 120 mm diastolic occur especially in older patients but are unusual in truly acute glomerulonephritis In some instances, especially in children blood pressures which cannot be regarded with certainty as abnormally high are seen in retrospect when the normal value is known to have constituted slight but definite hypertension for the individual

While in many cases the arterial tension is consistently elevated in others it fluctuates greatly As in essential hypertension the tendency is for the pressure to be higher toward evening

The elevation in blood pressure may be found at the very onset of the disease or it may come on gradually after the edema hematuria etc are well established It was long ago found by Mahomed[3] and Riegel[4] by means of sphygmographic studies that what they took to be increase in arterial tension may precede the edema and other phenomena of acute glomerulonephritis—the prealbuminuric stage of Mahomed This has been confirmed by a study of Koch[5] on scarlet fever convalescents He finds that during the period of scarlet fever when glomerulonephritis is most apt to occur a rise in blood pressure is very common The elevation of blood pressure may or may not be followed by proteinuria and hematuria and is usually very transient On the other hand Steiner[6] found that the changes in the urine in postscarlatinal glomerulonephritis precede the rise

in blood pressure Further investigations to decide the time relations of proteinuria and hypertension in postscarlatinal glomerulonephritis, a question of great theoretical significance would be highly desirable In my experience in acute glomerulonephritis due to infections of the throat urinary changes have antedated hypertension

The duration of hypertension in acute glomerulonephritis is variable Most often it runs parallel to the other phenomena of the disease But it sometimes drops to normal while the urinary abnormalities and edema are still present or what is rare but important the hypertension may outlast all other symptoms but slight proteinuria as the sole strong indication that the patient is not recovering completely but is entering the chronic phase of the disease As the patient recovers, the pressure usually drops gradually to normal or even below the normal but sometimes there is a considerable critical drop within a day

When the hypertension is well marked one often finds apart from the increased tension of the pulse an increase in the tonus of the arterial wall manifested by the radial artery remaining palpable in a segment from which the blood has been removed by compression This phenomenon (pseudo-arteriosclerosis of Moschcowitz) is often readily detectable in young patients without any peripheral arteriosclerosis but is not so well marked as in cases of longer standing in which hypertrophy of the media of the artery has occurred (Chapter 21)

HYPERTENSIVE ENCEPHALOPATHY —Hypertensive encephalopathy may occur In adults it appears in only a small proportion of the cases in children the cerebral attacks are more frequent but even here affect only a decided minority of the totality of patients Since the introduction of salt restriction full fledged hypertensive encephalopathy has become a rarity in glomerulonephritis The cerebral attacks occur almost exclusively in patients with arterial hypertension The elevation of blood pressure is usually great but in a small proportion of the cases almost always in children the hypertension is but moderate

The prodromes and symptomatology of hypertensive encephalopathy have been described in Chapter 11 Here it may be remarked that the cerebral seizures may come on at any time of the disease while the hypertension is still present and in very rare instances may even be the initial manifestations of acute glomerulonephritis By far the most common form of hypertensive encephalopathy is severe headache often accompanied by nausea and vomiting The most striking manifestation is the epileptiform convulsive seizure But other forms amaurosis delirium palsies etc occur in rare instances I have found that in addition to hypertensive headache slight manifestations—*formes frustes*—of hypertensive encephalopathy are decidedly more common in acute glomerulonephritis particularly in children than has generally been realized They consist in the most variegated cerebral symptoms—transitory aphasia weakness of a limb or of one half the body sometimes accompanied by the Babinski sign slight impairment of vision paroxysmal dyspnea severe headache and vomiting etc Since I have been especially interested in the subject I have repeatedly seen these phenomena which because of their evanescent character can be elicited only by careful questioning and

frequent examination They can be recognized as manifestations of hypertensive encephalopathy by their association with rises in blood pressure in the absence of any considerable retention of urinary constituents in the blood, and seem to be of little prognostic significance

Death during a single convulsive seizure is very rare But there is grave danger if the attacks follow one another rapidly which is likewise rare under modern treatment Judging by the older literature such repeated convulsive seizures were more common at the time when salt was not restricted and fluids were forced The chief danger during a convulsive seizure is sudden cardiac failure If the episode is survived, it may be followed by distinct improvement in the general course of the disease The rare amaurosis, transitory palsies aphasia etc clear up rapidly and completely if the patient does not die

HYPERTENSIVE RETINOPATHY —The typical picture of hypertensive retinopathy (p 368) is rare in acute glomerulonephritis and indicates a very severe case with a serious prognosis It occurs only in the presence of severe hypertension But it was pointed out in Chapter 12 that such cases can recover with complete healing of the retinal lesions, though this is extremely rare It was also stated (p 368) that less marked changes in the fundus oculi are not rare in acute glomerulonephritis With marked hypertension narrowing of the arterial blood columns may be evident Dr H A Derow (personal communication) has observed compression of the veins at the arterio venous crossings which disappeared with subsidence of the hypertension Small retinal hemorrhages are not uncommon and seem to be of little significance they are probably analogous to cutaneous petechiae

THE HEART —Goodhart[7] long ago pointed out that cardiac dilatation and failure may develop and even prove fatal in postscarlatinal nephritis Only in recent years however, has it been widely realized that heart failure is one of the great dangers in the early days of acute glomerulonephritis Clinical evidences of cardiac insufficiency were present in one third of Master's[8] and over two thirds of Whitehill's[9] patients and in half the children studied by Lyttle[10] Burke and Ross[11] found acute glomerulonephritis the most common cause of congestive failure in the Children's Hospital of Washington In my experience heart failure has been responsible for the majority of the few deaths in the first days of the disease It may be precipitated by the convulsions of hypertensive encephalopathy Pleural effusion may add to the embarrassment of the heart and augment dyspnea Heart failure in acute glomerulonephritis has greatly diminished in frequency and severity since salt restriction has been generally practiced

In the genesis of heart failure in acute glomerulonephritis two factors are concerned—hypertension and myocardial damage In most instances hypertension is present and presumably plays a part in producing the cardiac insufficiency This seems highly probable in the exceptional cases in which a steep rise in pressure is followed by acute left ventricular failure with pulmonary edema

There are also cases of acute glomerulonephritis in which the heart fails with little or no rise in blood pressure Here the factor of myocardial

damage is presumably predominant.* By taking serial electrocardiograms Master, Cossio[12] and their associates found electrocardiographic abnormalities in a high proportion of patients with acute glomerulonephritis. The most frequent evidences of *myocardial damage* are low or inverted T_1, depression or elevation of the S-T segment, changes in the QRS indicative of intraventricular conduction defect, and protraction of the Q-T interval revealing prolongation of electrical systole. Changes in the P wave may occur. Arrhythmias are rare. La Due and Ashman found Wilson's[14] ventricular gradient deviated to the right in 41 and to the left in only 1 of 101 patients; they attribute the right deviation to a combination of hypertension of acute onset and cardiac dilatation. The electrocardiographic changes generally disappear quickly after improvement, but sometimes a negative T_1 persists for weeks.

The cause of myocardial damage in acute glomerulonephritis is not clear. Heart failure and electrocardiographic changes may occur at a stage when there is little or no azotemia or abnormality in the K, Na, Cl or Ca content of the plasma. In febrile cases the myocardium may be damaged by toxemia, but this is hypothetical. The muscle fibers are sometimes separated by edema, and very rarely arteritic changes are seen. Most investigators have found no adequate anatomical basis for the cardiac insufficiency (*cf* Whitehill *et al*[9]). Recently Gore and Saphir[15] observed what they term myocarditis in 16 of 160 necropsies on acute and subacute glomerulonephritis. They describe widespread serous effusion between the muscle fibers containing relatively sparse cellular elements; muscle necrosis was rare. The extent to which such interstitial edema participates in the production of heart failure seems problematical.

Alwens and Moog[16] have shown by radiographic studies that in most cases the cardiac area is enlarged to the left at a very early stage. They find that the enlargement in the early stages is due to a combination of acute dilatation of the left ventricle with, as a rule, slight hydropericardium. Alwens and Moog were able to demonstrate hypertrophy of the left ventricle only after the hypertension had existed for several weeks. Guggenheimer[17] likewise observed in cases of war nephritis that it takes about four or five weeks before left ventricular hypertrophy is found. On the other hand Friedlander[18] found anatomically that cardiac hypertrophy is often present in cases of postscarlatinal glomerulonephritis that died in the second to the fourth week of the disease. Thus early hypertrophy is evidently not demonstrable by clinical or radiographic methods. The question also arises whether what was regarded as hypertrophy so early in the disease was not to at least some extent increase in mural thickness and weight due to interstitial edema.

* However, it is to be remembered that increase in peripheral resistance is not necessarily revealed by *rise* in arterial pressure when myocardial insufficiency is present, for the latter may have already caused a drop in pressure which completely conceals the existence of a *degree of* arteriolar constriction that would result in hypertension with a strong heart. Moreover, the work of the heart in acute glomerulonephritis is often doubtless *increased* by hydremic plethora resulting from oliguria (and sometimes abetted by *forcing* of fluids). By hematocrit readings and plasma volume measurements with *Evans blue* Cardozo[4] found evidences of hydremic plethora in the first days of the disease.

In many cases hypertension does not engender symptoms of cardiac insufficiency, and physical examination of the heart reveals no abnormality. In such patients the pulse is occasionally slow, even down to 50 per minute, but more often bradycardia is not present and there may be tachycardia corresponding to such fever as may exist.

In other patients, with or much less often without hypertension, evidences of a slight degree of cardiac insufficiency make their appearance. These consist in mild or moderate dyspnea and sometimes palpitation or inability to lie on the left side. Dyspnea may be an initial symptom. Objectively, the findings are tachycardia, perhaps slight enlargement of the heart to the left and a systolic murmur at the apex. Relative weakness of the left ventricle may be indicated by the fact that the pulmonic second sound is as loud as or louder than the aortic second sound, despite the presence of hypertension. All of these signs disappear rapidly if the patient improves.

On the other hand *there are unusual cases in which cardiac insufficiency is very severe and dominates the clinical picture*, death may occur with the typical phenomena of cardiac failure. The heart may give way with startling suddenness either out of a clear sky or following a convulsion. At the onset the picture is generally that of typical left ventricular failure (see p. 777). There is agonizing dyspnea, orthopnea and cyanosis. The heart rate becomes very rapid, there is gallop rhythm and a functional systolic murmur at the apex and the pulmonic second sound is accentuated, sometimes enlargement to the left can be demonstrated within a relatively short period. Moist rales are generally to be heard at the bases of the lungs and at any time outspoken pulmonary edema with its characteristic auscultatory signs and pink, foamy, albuminous expectoration may appear. In some instances the blood pressure falls, in others it rises (see *Hochdruckstauung*, p. 789). There may be pulsus alternans. In those cases which are seen during this stage of predominant left ventricular failure there is neither peripheral edema nor notable swelling of the liver and the veins are not distended. In some such cases death from pulmonary edema may be appallingly rapid—*the hyperacute asystole of the French*. But more often there are added signs of right ventricular failure—enlargement of the liver, distention of the veins with notable rise in venous pressure * and often cardiac edema—to the consequences of insufficiency of the left heart. In fact, some cases are seen first when signs of failure of both ventricles are present, the right ventricle sometimes gives way close on the heels of the left with resultant rise in venous pressure and swelling of the liver. But there are also patients in whom the symptomatology for days is that of isolated failure of the left venturcle, the dominant feature being attacks of cardiac asthma (see p. 778) with or without demonstrable evidences of pulmonary edema.

* Distention of the veins and rise in venous pressure may not always be indicative of a high degree of right ventricular failure in acute glomerulonephritis. It was mentioned above that there is evidence of hydremic plethora during oliguria in some cases of acute glomerulonephritis. This may be the explanation of the occasional presence of venous engorgement in the absence of signs of left ventricular failure and pulmonary engorgement.

THE URINE —The typical urinary findings in acute glomerulonephritis consist of oliguria hematuria proteinuria and cylindruria

The urinary volume is diminished at the start and while the disease is advancing The daily volume is extremely small in very severe cases anuria may supervene which is always a very dangerous omen It usually quickly leads to death but we mentioned a case above in which the anuria lasted fourteen days before the fatal outcome Oliguria is as a rule most marked at the onset and in the first few days when edema is accumulating but the urinary volume may be small even without edema The daily output is generally about 400 to 700 cc The urinary volume usually but not always diminishes before the onset of convulsions There are several causes for the oliguria of acute glomerulonephritis

1 The primary cause is impairment of filtration due to thickening of the walls of the loops and sometimes also to obturation of their lumens For reasons which remain to be elucidated the diminution in the volume of filtration is not counterbalanced by an equal decrease in tubular reabsorption of water

2 If the conception of generalized capillary damage in acute glomerulonephritis is valid the resultant prerenal deviation may contribute to the oliguria

3 Cardiac insufficiency may add to the oliguria

4 Vomiting diarrhea or fever may likewise diminish the urinary volume

One of the first signs of improvement is generally an increase in urinary volume which may rise to over 2000 cc daily as edema is being resorbed

Hematuria —Hematuria is present in almost every case leading to the name acute hemorrhagic nephritis In most instances there is sufficient blood present to be detected with the naked eye the urine being colored various shades in accord with the amount of blood present When there is much blood the urine is correspondingly red when little a reddish or greenish dirty brown Often the urine appears smoky or like water in which meat has been soaked (*fleischwasserachnlich* of the Germans) In other cases or at other times the hematuria may be only microscopic In some very severe cases there is little blood in the urine though this is rare In most instances marked hematuria is not of long duration diminishing after a few days or at most weeks But the microscopic hematuria may be very protracted a few red cells are often found in the sediment after the proteinuria has cleared up completely and may last for many months without necessarily indicating that the renal process is becoming chronic Improvement in the renal condition is sometimes accompanied by temporary increase in hematuria presumably indicating the reentry of blood into previously impermeable glomerular loops

Microscopic examination of the sediment shows in addition to well formed red cells shadows of cells from which the hemoglobin has been extracted There are often red cell casts There may be also clumps of hemoglobin Bittorf[19] has described 3 cases of recurrences in acute glomerulonephritis in which hemoglobinuria alone was present In each instance the recurrence followed exposure to cold Since there was no evidence of hemolysis in the arm blood the hemoglobin must have been freed in the kidneys

The source of the hematuria in acute glomerulonephritis is presumably rupture into the capsular space of glomerular loops which are injured but still permeable

Proteinuria —Proteinuria is present in all but extremely rare instances As a rule, it does not surpass 0 2 to 0 4 per cent, but in unusual cases it may exceed even 2 per cent The amount of protein does not necessarily run parallel to the severity of the case The proteinuria usually outlasts the other notable phenomena of the disease though often microscopic hematuria is present long after the protein reactions become negative During convalescence the proteinuria sometimes becomes distinctly orthostatic in type appearing only when the patient leaves the bed and the urinary volume falls as a result of decreased renal blood flow (p 122) This may last for months The acetic acid body may be present long after the urine no longer clouds on boiling

A small number of cases of acute glomerulonephritis have been published in which proteinuria was absent either entirely or for a considerable time after the other features (edema hypertension etc) had appeared Henoch[9] long ago reported 3 cases of postscarlatinal glomerulonephritis with edema in which proteinuria was either absent or but intermittently present in 2 of the cases the diagnosis was verified at necropsy The same was observed by Nonnenbruch[1] and Guggenheimer[17] in war nephritis Wickbom[72] also studied 3 cases with an acute clinical picture characterized by hypertension, edema hematuria, and cylindruria in which proteinuria was either absent or intermittent Following a sore throat a sixteen year-old girl studied by Crofton and Truelove[3] developed edema and a blood pressure of 182/110 mm no urinary abnormality was detected except proteinuria on the eleventh day Among 248 cases of acute nephritis Allesandri and Rosihman[4] observed 6 without or with only minimal urinary changes in 1 of these necropsy revealed acute glomerulonephritis

The Urinary Sediment —The urine almost always deposits a heavy sediment, usually brownish red in color With severe hematuria it may be bright red In addition to numerous red cells and frequently large quantities of urates the sediment contains the following elements

Casts are practically always present In the earliest stage hyaline and blood casts are usually the only varieties found but later granular epithelial, sometimes fatty and rarely waxy casts appear Casts containing doubly refractile lipoids are not found in the first period their presence speaking for a considerable duration of the process with marked secondary tubular lesions

Cylindroids are generally also present and may be particularly abundant during convalescence as the last urinary sign of the disease (Lichtwitz[4])

Leukocytes almost always occur in numbers greater than that corresponding to the blood present they are as a rule particularly numerous in the first period

Epithelial cells are usually few in number or absent at first later with the onset of tubular degeneration they appear in large numbers

Specific Gravity of the Urine —When renal function is little impaired the specific gravity of the urine is high (1022 to 1032) because there is prerenal deviation of water into the tissues to form edema and the density

is elevated by the admixture of blood and protein In such urine the concentration of urea is high but that of chloride is very low, for the edema fluid contains a higher proportion of chloride than the blood The specific gravity is likewise high at the stage in which glomerular filtration is diminished but tubular function is relatively intact The association of high specific gravity of the urine with azotemia is characteristic of uncomplicated impairment of glomerular filtration This stage of isolated slowing of filtration may last from only a day or two to the entire duration of the disease When tubular function also becomes impaired as it almost always does in other than mild cases the specific gravity of the urine falls so that when a concentration test is carried out the patient may not be able to exceed a specific gravity of 1 015 or even 1 010 in such urine the concentration of urea and other substances is correspondingly low The passage of small volumes of urine with low specific gravity in an edematous patient is immediately indicative of impaired tubular function It should be remembered that copious admixture of blood or massive proteinuria raises the specific gravity

Renal Function —The effect of acute glomerulonephritis on renal function varies greatly From the clinical point of view three functional states may be differentiated they often follow one another as successive stages in the evolution of the disease

1 *Relatively Intact Renal Function* —There may be little impairment of renal function the patient can form both a highly concentrated and very dilute urine the urea clearance is tolerable and there is no nitrogen retention in the blood This may occur at the start and it may persist throughout the course of cases the diagnosis of which is definitely established by the urinary changes nephritic edema and even hypertension

2 *Impaired Glomerular Filtration With Relatively Intact Tubular Function* —In this state there is oliguria with high specific gravity of the urine the former is due to decrease in glomerular filtration and the latter affords evidence that the concentrating ability of the tubules is little impaired The diminution in glomerular filtration has been demonstrated by measurements of inulin clearance (p 578) The oliguria may be so marked that despite the high concentration of the urine there is pronounced nitrogen retention The nitrogen retention may have the characteristic that the urea is greatly elevated while there is little change in the creatinin This is presumably due to urea being eliminated solely by glomerular filtration while creatinin is excreted not only by glomerular filtration but also by tubular secretion Since tubular function is good the creatinin content of the blood does not rise as much as does the urea Impaired glomerular filtration with intact tubular function is perhaps a manifestation of changes in the glomerular loops sufficiently pronounced to hamper filtration but not greatly obstructing blood flow through the loops so that the blood supply to the tubules remains fairly adequate Isolated impairment of glomerular filtration in acute glomerulonephritis may be very transient or last even as much as two weeks it is succeeded either by improvement or by the addition of impairment of tubular function

3 *Combined Impairment of Glomerular Filtration and of Tubular Function* —Clinically, damage to tubular function is revealed by hyposthenuria Presumably, at this stage the glomerular lesion is such that it not only hampers filtration but also impedes blood flow through the glomeruli to such an extent that the blood supply to the tubules is inadequate

For the impairment of renal function to lead to death from true uremia during the acute stage is decidedly unusual, many of the cases that are considered as such are really instances of hypertensive encephalopathy or cardiac failure Uremia occurred in but 19 of Barasch's[6] 232 cases of postscarlatinal glomerulonephritis and in this number are included some instances of hypertensive encephalopathy When uremia does supervene, it presents the same picture as when due to other causes—nausea vomiting, apathy deepening to stupor and then to coma, muscular twitchings, etc

INDIVIDUAL RENAL FUNCTIONS —In recent years a number of measurements of the discrete renal functions have been carried out in acute glomerulonephritis though unfortunately few in the first days of the disease These have revealed depression in glomerular filtration greater than in renal blood flow and in such tubular functions as have been measured

Measurements of *renal blood flow* by the diodrast or PAH clearance (Earle[7] *et al* and others) have most often revealed a decrease, in some instances to very low levels However observations by Earle[7] Bradley[8] and others show that some patients pass through a stage of renal hyperemia with increased blood flow Bradley's observations may be accepted as unequivocal inasmuch as he corrected the PAH clearance by the PAH extraction obtained by catheterization of the renal vein

Glomerular filtration (inulin or mannitol clearance) is subnormal in the large majority of instances The depression in glomerular filtration is greater than in renal plasma flow with the result that the *filtration fraction* is below normal Greater diminution in glomerular filtration than in renal blood flow would be anticipated to result from lesions which start in the walls of the glomerular loops

Observations with regard to *tubular functions* have varied probably largely in accord with the stage of the disease Bradley found subnormal extraction and maximal tubular excretion of PAH, revealing functional impairment of the tubules Contrariwise in 1 case of acute and 3 of subacute glomerulonephritis Cargill[29] observed PAH extraction within normal limits In Earle's observations maximum excretion of PAH was unaffected in mild cases and when depressed was less so than glomerular filtration Earle *et al* found that glucose reabsorption is relatively little affected in acute glomerulonephritis and that ammonia excretion is not decreased in the early stages of the disease although it becomes so later As stated above the clinical and anatomical findings indicate strongly that patients with acute glomerulonephritis pass at the onset through a stage in which glomerular filtration is diminished while tubular functions are still intact It would be desirable to have this conception fortified by measurements of the individual functions in the *first* days of the disease

Low *oxygen consumption* of the kidney despite normal renal blood flow was found in glomerulonephritis by Cargill and Hickam[30] However none of their cases was of less than five weeks duration

Blood Chemistry.—The chemical changes in the blood in renal insufficiency resulting from acute glomerulonephritis do not differ from those in other varieties of renal failure except for the above mentioned instances in which the urea content of the blood rises in the absence of creatinin retention. Because of the usually brief duration of impairment of renal function, the fact that the patients are kept on a restricted diet and the formation of edema which stores urinary constituents in about the same concentration as the blood, it is unusual for high degrees of retention to develop. But in some instances this does occur. With anuria, of course, maximal retention develops.

The concentrations of sodium and of chloride in the blood vary greatly. De Wesselow[31] long ago observed that the serum chloride level may be either elevated or depressed. There are a number of factors influencing the sodium and chloride concentration. Impaired renal function and the ingestion of salt by patients whose diet has not been properly restricted elevate the sodium and chloride. The absorption of edema (which has a higher chloride content than the blood) tend to raise the chloride of the blood. On the other hand, the formation of edema, vomiting and restriction of salt in the diet tend to lower it. Because of these various conflicting influences the sodium and chloride content of the blood may oscillate rapidly in the same patients. Hyperpotassemia is rare in acute glomerulonephritis and occurs only when the patient is anuric or almost so. Rarely, vomiting and diarrhea result in hypopotassemia.

The blood volume is likewise controlled by opposing influences. The formation of edema, therapeutic restriction of fluid and vomiting tend to concentrate the blood while impairment of glomerular filtration, ingestion of water and absorption of edema tend to dilute it and produce hydremia. The progressive anemia which develops also favors relative hydremia. Brown and Rowntree[32] long ago found by means of the Congo-red method for determining plasma volume that in acute and subacute glomerulonephritis with edema the *plasma* volume averages within normal limits (51.9 cc. per kilogram body weight), though there is considerable variation in either direction (from 36 to 64 cc. per kilogram). However they found that the *total* blood volume averaged well below the normal because of the decreased red cell volume, though here also some cases were normal. Lichtwitz[33] observed increased blood volume in several cases of very early glomerulonephritis. Litzner[34] also found the blood volume increased in acute glomerulonephritis when hypertension was present. Nonnenbruch[34a] observed that while in most edematous nephritics the blood is either normally concentrated or hydremic, in some cases the concentration is abnormally high. In 18 patients with acute glomerulonephritis Cardozo[35] found evidences of hydremia in the first days: the hematocrit and serum protein concentration were low and returned to normal in a fortnight. With Evans blue, he found that the plasma volume was higher in the early days than later. It would appear that in the early days of acute glomerulonephritis with severe oliguria there is usually increased blood volume with hydremia, but that later in the course of the disease opposing influences may decrease or increase the blood volume.

The total protein content of the plasma is within normal limits in the early stages of acute glomerulonephritis Examination of the individual protein fractions usually reveals the albumin and globulin to be approximately normal in the initial stages, but sometimes there is increase in globulins and in fibrinogen (Starlinger[37]), the latter is doubtless to be regarded as a manifestation of the infection The normal concentration of plasma albumin shows that edema in acute glomerulonephritis is not due to diminished colloid osmotic pressure of the plasma as in chronic nephrosis and often in subacute and chronic glomerulonephritis It usually takes at least several days of loss of large quantities of albumin in the urine to diminish plasma albumin notably

The blood cholesterol and other lipids are likewise normal in acute glomerulonephritis in contrast to the later stages and chronic nephrosis

THE BLOOD CELLS —Despite the pallor of the patients there is no anemia in the very first stages, unless it is present as a result of the primary infection Later on secondary anemia generally develops and may become very severe (Chapter 21) Nor is the white cell count always influenced by the renal process though there is often moderate polymorphonuclear leukocytosis when the onset is febrile The sedimentation rate of the red blood cells is usually accelerated

THE LUNGS —Diffuse bronchitis causing annoying cough is not uncommon In many fatal cases of war nephritis Dunn and MacNee[1] found focal pulmonary lesions of peculiar histology which they considered as frequently responsible for severe dyspnea The latter is, however most often due to left ventricular failure Pneumonia was formerly a fairly common complication particularly in children Pospischil[38] found it in 11 per cent of his cases of postscarlatinal glomerulonephritis Since penicillin, pneumonia is rare The occurrence of pulmonary edema as a result of cardiac failure was mentioned above

GASTRO INTESTINAL SYMPTOMS —Nausea vomiting and either diarrhea or constipation are common at the onset in children They may also occur though less often when there is a very abrupt onset in adults and and yet not be a manifestation of uremia In such non uremic cases the vomiting may perhaps be interpreted as reflex from the acutely swollen kidney akin to the reflex vomiting in nephrolithiasis Or it may be due to hypertensive encephalopathy Nevertheless during the course of acute glomerulonephritis vomiting should always raise the suspicion of uremia

THE SKIN —The patients are usually though not always pale The pallor is not entirely due to anemia for it occurs in patients with normal amounts of hemoglobin Volhard[39] considers the pallor a manifestation of the universal vasoconstriction which causes the hypertension but this is probably not the whole story for it also occurs in chronic nephrosis where there is no reason to believe that vasoconstriction is present Quite probably slight degrees of edema contribute to the pallor by increasing the opacity of the skin During the formation and persistence of the edema the skin is often preternaturally dry It has been found that at this time the insensible perspiration is diminished, and it is difficult to make the patients sweat by diaphoretic measures

OTHER SYMPTOMS —*Fever* of moderate degree may be present particularly at the beginning In exceptional cases, the onset is with high fever Quite probably when fever is present it is due more to the primary infection than to the renal process for other equally severe cases have a completely afebrile course Postscarlatinal glomerulonephritis is often marked by fever up to 103° F or more during the first few days though the child may have been afebrile for two weeks previously Even here it is doubtful if the glomerulonephritis is the cause of the fever for the onset of the renal disorder in such cases is often accompanied by other features of the second sickness such as sore throat lymphadenitis etc Convulsive seizures are generally accompanied by fever In adults most cases are completely afebrile after the first few days or during the entire course unless pneumonia or another febrile complication occurs

Pain in the lumbar region is very common at the onset and may radiate to the genitalia and thighs as in nephrolithiasis It is often accompanied by tenderness in the costo-vertebral angles The pain and tenderness have been thought by some to be due to stretching of the renal capsule by the swollen kidney Bradley[38] has suggested that the hyperemia he demonstrated in some cases (p 578) may be concerned in the loin pain Another possible explanation is that the pain is due to inflammatory involvement of the capsule the actual existence of which is occasionally seen both at necropsy and during decapsulation operations

Urgency and frequency with the painful passage of small quantities of urine are likewise not uncommon early complaints The explanation of these symptoms is also not clear they may perhaps be connected with the congestion of the mucous membrane of the urinary passages that is occasionally seen at necropsy Nocturia is very common

In very rare cases the *spleen* is sufficiently enlarged to be palpable This was not as rare in war nephritis The splenomegaly is presumably a manifestation of the primary infection Occasionally the *liver* is enlarged sometimes this is due to cardiac weakness but in other cases this explanation does not seem to hold and increased blood volume (p 579) may be concerned

Occasionally *purpuric spots* appear in small numbers While thrombopenia is often present (see Pakozdy[40]) it is rarely marked With improvement the platelets rise to even above the normal accompanied by an increase in the number of young granulocytes as evidence of hyperactivity of the bone-marrow (Doenecke[41]) The tourniquet test is often positive Whether this indication of increased fragility of the capillaries is correlated with injury to the capillaries concerned in producing the edema is so far as I am aware not known At this early stage of the disease there seems to be no reason to incriminate vitamin deficiency as the cause of bleeding

Epistaxis is not infrequent capillary injury thrombopenia and hypertension are factors that may be concerned in producing the nosebleeds

DIAGNOSIS OF ACUTE GLOMERULONEPHRITIS

The diagnosis presents no difficulty in the typical case in which the urinary abnormalities are accompanied by edema or hypertension or both

But even under such circumstances, the prognostically important question may arise whether the present illness is truly acute glomerulonephritis or an acute exacerbation of a chronic process. The presence of well marked cardiac enlargement in the absence of symptoms of myocardial insufficiency speaks strongly for chronic glomerulonephritis, for when the heart is notably enlarged in acute glomerulonephritis there is usually also other evidence of cardiac failure. On the other hand, cardiac hypertrophy or dilatation is not demonstrable by physical or radiographic examination in many cases of chronic glomerulonephritis, particularly in the nephrotic type of the disease. Very great hypertension, above 200 mm systolic pressure, speaks in favor of an old renal lesion, though this is by no means unequivocal, for such pressures are occasionally observed in acute glomerulonephritis. Of course lower pressures occur in both the acute and the chronic stage. The presence of sclerotic peripheral or retinal arteries also argues for a process of long standing, though here the occurrence of spasms of the arterial wall in acute cases must not be forgotten. None of the criteria are absolute, and in some cases the differentiation between acute glomerulonephritis and an acute exacerbation of a chronic process is impossible; where the clinical evidence seems to speak strongly in favor of the former, chronically diseased kidneys may be found at necropsy.

When microscopic or macroscopic hematuria appears during an acute infection, such as tonsillitis, erysipelas, pneumonia, osteomyelitis, etc., the differentiation between acute glomerulonephritis and focal nephritis arises. The presence of edema, hypertension or impairment of renal function speaks immediately for glomerulonephritis. If the urinary findings appear several days or more after a sore throat has subsided, they are more likely to be the result of true glomerulonephritis, but during the height of the infection either may arise. It should be remembered that it is extremely rare for glomerulonephritis to appear in the course of infections other than streptococcal. In general, therefore, it is wise to consider hematuria in infections due to bacteria other than streptococci or viruses as not due to diffuse glomerulonephritis unless proved to be so by the appearance of nephritic edema or hypertension—an exceedingly rare event.

In subacute bacterial endocarditis hematuria may be due to gross infarction, multiple glomerular thrombosis or diffuse glomerulonephritis. The presence of nephritic edema or hypertension is evidence for diffuse glomerulonephritis, though their absence does not speak against it. In fact, in the vast majority of instances of diffuse glomerulonephritis complicating subacute bacterial endocarditis there is neither hypertension nor edema. Impairment of renal function is also very strong evidence in favor of diffuse glomerulonephritis, for it is excessively rare in multiple glomerular thrombosis.

Acute glomerulonephritis may also be confused with periarteritis nodosa involving the kidney. The differentiation depends on the presence or absence of the positive criteria of arterial disease in other organs; marked eosinophilia is present in some, though not all, cases of periarteritis nodosa, but is absent in glomerulonephritis. It should be remembered that periarteritis implicating the renal arteries may produce hypertension. The

differentiation from the wire loop lesion of Libman-Sacks disease is to be borne in mind hypertension is rare in the latter

PROGNOSIS OF ACUTE GLOMERULONEPHRITIS

The outlook in acute glomerulonephritis is in general comparatively good for a disease which often presents very alarming manifestations Of the three outcomes—complete recovery chronicity and death during the acute stage—recovery is more common than chronicity while death during the acute stage is exceptional Of children the large majority recover completely while with increasing age at the time of onset the proportion that becomes chronic rises greatly

Postscarlatinal glomerulonephritis usually lasts from two to six weeks However there are mild cases that clear up completely or remain with but light urinary abnormalities within a week In other instances the proteinuria persists for several months The longer the proteinuria continues the greater the chance of a chronic irreversible process developing but complete recovery may occur after a year and even in rare instances after two years of proteinuria

All evidence indicates that the proportion of cases of postscarlatinal glomerulonephritis that terminates in chronic renal disease is very small Jaeger[45] observed only 2 cases of proteinuria of more than six months duration in 65 cases of scarlatinal nephritis that had developed in the hospital and 3 chronic proteinurias among 12 patients who were admitted already suffering from scarlatinal nephritis Hansberg[46] found that of 254 persons who had had scarlatinal nephritis from one to ten years before the examination only 1 had proteinuria of five years duration Rosenfeld and Rechenstamm[47] examined 92 individuals who had had scarlatinal nephritis from six to ten years previously and of whom 52 still had proteinuria at the time of discharge Ten had proteinuria 7 casts and only 1 hypertension From these figures it is seen that one may assure parents of children who have recovered from postscarlatinal glomerulonephritis that the chances of chronic renal disease are extremely small However there have been said to be very rare cases in which after seemingly complete recovery with negative urine glomerulonephritis appears years later, such a case is described by Holt[48] Of course it is questionable whether such instances are not totally independent of the scarlatinal disease

In the unusual cases that become chronic the typical picture of chronic glomerulonephritis develops It may terminate fatally within months or years I have seen cases in which proteinuria has persisted for forty years

Death during the acute stage of postscarlatinal glomerulonephritis occurs in a small proportion of cases Barasch[49] observed 14 deaths in 232 patients Jaeger[45] 4 in 65 cases which developed in the hospital and 4 in 12 patients admitted with the renal complication Apparently however there are or were epidemics in which the mortality is much higher Thus Bartels[50] remarks that all 13 cases of scarlatinal nephritis which he treated in the year 1863 terminated fatally but that he did not see a fatal outcome for several years thereafter Presumably such differences go hand in hand with the known variations in virulence of scarlet fever in different years The danger signs and causes of death will be discussed below as they are

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Acute glomerulonephritis complicating purpura seems to be a particularly dangerous variety for of Osler's[59] 14 collected cases, 5 ultimately died of uremia

When acute glomerulonephritis supervenes in *subacute bacterial endocarditis* it is very apt to become chronic (Baehr and Lande[60]) Death may occur from uremia or more often from some manifestation of the primary disease

The chief *sources of danger* in acute glomerulonephritis are acute myocardial insufficiency resulting in pulmonary edema uremia, and hypertensive encephalopathy Extreme oliguria is always a danger signal, foreboding uremia if not relieved Sometimes diminution in the volume of urine precedes hypertensive encephalopathy Complete anuria for any considerable length of time is almost always fatal though patients have been known to recover after two days of anuria I saw one who did so after four such days Single convulsive seizures do not notably cloud the prognosis if survived and may even be followed by improvement as though a crisis had occurred But repeated convulsive seizures are very apt to terminate fatally In former times edema of the larynx was apparently not uncommon as a cause of death but is scarcely seen nowadays since salt restriction has been introduced Pneumonia and other infections were formerly a menace but at present are rarely dangerous

The intensity of the proteinuria hematuria or edema is of little aid for they may all be very marked and yet the patient recover completely within a few weeks or months It has seemed to me that the chances of chronicity are less in those patients who have profuse hematuria but relatively little proteinuria than in those in whom hematuria quickly subsides and is followed by massive proteinuria The longer the proteinuria or edema persist the greater the chance of the process becoming irreversibly chronic The *blood pressure* is a more valuable guide When the arterial tension is very high the case is undoubtedly severe and the outlook is always in doubt until the pressure comes down Persistence of hypertension indicates a process that is very likely to become chronic It should be borne in mind however that in rare cases which rapidly die of uremia there is no hypertension

Often hyposthenuria is the last evidence of the disease to disappear Inability to form a hypertonic urine often lasts for months after proteinuria has disappeared and does not forebode chronicity In its last stages proteinuria is often orthostatic the appearance of a definitely cyclic proteinuria in my observations has presaged complete recovery Rubin[61] and his associates found in children that while the routine urinalysis became normal in the average time of thirty seven days the Addis count for erythrocytes took an average of one hundred and twenty days to become normal They found that the erythrocyte sedimentation rate took an average of eighty-six days to return to normal

Contrary to rheumatic fever once a patient with acute glomerulonephritis has recovered recurrence is almost unknown I am not sure that I have ever observed a patient who recovered *completely* from acute glomerulonephritis and had a second attack Loeb *et al*[62] followed 10 patients with healed glomerulonephritis through subsequent hemolytic streptococcic infections while two had hematuria none developed significant proteinuria

much the same in the different etiological varieties of acute glomerulonephritis

Acute glomerulonephritis following tonsillitis and other infections of the respiratory tract also terminates in recovery in most instances, but in these patients the incidence of chronic renal disease is higher than after scarlet fever Possibly, particularly after throat infections the reason is that an infectious focus may persist and continue to injure the kidney but this explanation does not apply to all cases (p 601) In adults the frequency of a chronic process is decidedly greater than in childhood but it must be considered that seemingly initial attacks in older people may in reality be recrudescences Death during the acute stage is more likely to occur in children than in adults Thus, Clausen[47] had 21 deaths in 102 cases of acute glomerulonephritis in children, of which 26 were postscarlatinal Of the 21 deaths 10 were from uremia, (presumably including hypertensive encepholopathy) 4 pneumonia 2 cardiac failure and 1 whooping cough Of 38 cases of acute glomerulonephritis in children followed for a year or longer by Lyttle and Rosenberg [48] 30 were cured 4 became chronic and 4 died of the 4 deaths 2 were due to uremia, 1 each to sepsis and pneumonia Of 230 children with acute glomerulonephritis seen by Kohn,[49] 5 per cent died during the acute stage of the remainder followed from one to twenty years 85 per cent recovered completely 5 per cent developed progressive chronic glomerulonephritis and the other 10 per cent renal disease with proteinuria that did not progress within the period of observation Burke and Ross[50] studied 90 children with acute glomerulonephritis, 64 recovered completely, 3 died of heart failure and 3 developed chronic renal disease Most of the few deaths in children that I have seen during the first days of the disease have likewise been of heart failure Lyttle[10] reported a mortality rate of 9 4 per cent in 722 cases of acute nephritis in children observed by different clinicians

My experience in adults with definite glomerulonephritis has been that hardly more than half the patients recover completely Longcope[51] found that only 42 5 per cent of 134 patients with acute glomerulonephritis recovered completely Similar observations were made by Murphy and Peters [52] Only a small proportion succumb during the acute stage while the others remain with at least proteinuria to show that the kidneys have not healed completely

In *trench nephritis* the mortality during the acute stage was low Maclean[53] had 4 deaths in 500 cases Keith and Thomson[54] 2 3 per cent mortality in 300 cases and Toemessen[55] 3 per cent in 254 cases However a considerable proportion of the patients developed chronic glomerulonephritis Thus Hume and Nattrass[56] studied 281 men who suffered from acute nephritis during the World War They found that while 45 5 per cent show no evidence of renal disease 9 5 per cent have advanced chronic nephritis and 2 5 per cent have died of the disease The remaining 45 per cent show evidence of some permanent damage to the kidney and are probably developing the disease ' Almost identical observations were made by Gros [57] only 44 6 per cent of whose patients with war nephritis recovered completely During World War II, Brod[58] likewise observed a high incidence of chronicity

extensive investigations of Pospischill and Weiss[34] who fed one-half of 2373 scarlet fever patients with a milk diet while the other half got the usual meat ration The incidence of glomerulonephritis was almost the same in both groups but the general medical and physical state of the children who were given meat was far the better Identical results were obtained by Jochmann[35] in 1000 scarlet fever patients Dietary restriction therefore is not a prophylactic of postscarlatinal glomerulonephritis, and the same probably applies to glomerulonephritis following other infections From the point of view of preventing glomerulonephritis there is no reason why the convalescent from scarlet fever or sore throat should not have a full diet including ample meat and eggs indeed there is every reason why he should

General Management — The patient must be kept in bed throughout the acute stage of the disease although he may be allowed lavatory privileges Apart from the fact that leaving bed may entail exposure to cold the observation that assuming the erect posture increases the proteinuria and even the hematuria can very frequently be made The often difficult question of when to allow the patient to leave bed will be discussed below

Particular care should be taken that the patient is always kept warm and shielded as much as possible from respiratory infections Flannel garments are perhaps the best and at night the blankets should be adequate While sufficient ventilation is essential drafts must be avoided No disease requires more careful protection from cold than acute glomerulonephritis for the following three reasons

1 There is no doubt that cold is an important predisposing factor in the causation of the underlying infection in many cases of glomerulonephritis

2 There is experimental evidence that the vessels of the kidney react consensually with those of the skin and in view of the intense ischemia of the glomeruli so characteristic of acute glomerulonephritis it would seem that the renal vasodilatation that apparently accompanies cutaneous vasodilatation is much to be desired However it remains to be proved that the vessels of the diseased kidney react as they do in experiments on healthy animals

3 The increased elimination through a warm skin relieves the kidney of a certain amount of work though this is not quantitatively very significant

Sweating procedures were formerly popular in the treatment of acute glomerulonephritis but have lost much of their vogue in recent years In the chapters on Edema and Uremia it was seen that the quantities of potential urinary constituents thus eliminated through the skin was not sufficiently great to compensate for the frequently well marked weakening of the patient There would seem to be no rationale for the induction of diaphoresis in acute glomerulonephritis The same is true of vigorous massage which was formerly also used Ekgren[36] has observed that the latter may augment proteinuria

The bowels should of course be kept open and best somewhat loose but the vigorous purgation so popular in former days is to be avoided Mercurial cathartics should not be used because of their nephrotoxic potentialities to ischemic kidneys Magnesium sulphate should be avoided with marked azotemia (p 66)

TREATMENT OF ACUTE GLOMERULONEPHRITIS

The treatment of acute glomerulonephritis is largely symptomatic, for we have no means at our disposal to influence favorably the course of the lesions in the glomeruli and we are usually unable to influence the disease through combatting specifically the primary infection The high hopes entertained that sulfonamides and penicillin would accomplish the latter and cortisone or ACTH the former have not been fulfilled Nevertheless the increase in knowledge of the nature, and especially the pathological physiology, of acute glomerulonephritis in recent years has entailed more rational therapy, particularly dietetic While the opinion expressed repeatedly by Volhard[63] that no patient should die directly of acute glomerulonephritis is much more optimistic than justified by my personal experience, there is no doubt that a great deal can be done for the patient by careful attention to the details of treatment and the avoidance of all schematicism

PROPHYLAXIS —Data do not seem to be available to decide whether treatment of tonsillitis and other infections with antibiotics lessens the incidence of glomerulonephritis The point could be settled by treatment with antibiotics of alternate members of a large series of comparable infections, but such a series has not been published Many cases of acute glomerulonephritis are seen in which the causative sore throat was treated with adequate amounts of penicillin Glomerulonephritis seems to the writer to have greatly diminished in frequency in New York City in the past twenty years and is more common in the economically unfortunate groups but whether these differences are due to sulfonamides and penicillin or to a lesser incidence of causative infections remains to be decided

The important role in the etiology of acute glomerulonephritis played by infections of the lymphatic ring in the throat was indicated above The removal of *definitely diseased* tonsils and adenoids may therefore serve to prevent some cases of acute glomerulonephritis This of course does not mean the ruthless and wholesale removal of every tonsil large enough to be seen as is so commonly practiced but only those in which the evidence of infection seems clear-cut Unfortunately however the experience with glomerulonephritis is precisely that with rheumatic fever unabated progression is often seen despite technically adequate removal of the tonsils and many initial attacks are encountered where the tonsils have been removed completely years before Truly diseased teeth should likewise be removed but here also the unnecessary zeal of recent years should be avoided the same applies to the paranasal sinuses which are operated upon far too often

Osman[64] found that the administration of antiscarlatinal serum to patients with scarlet fever is of no value in the prevention of nephritis After the febrile period the convalescent should be carefully protected from cold and respiratory infections for a period of four weeks In fact some authorities keep convalescents from scarlatina in bed for this period, but there is no evidence that this helps to prevent renal complication In the past, great stress has been laid on the value of a milk diet as a prophylactic of postscarlatinal glomerulonephritis This belief was shattered by the

3 Carbohydrate and fat are burnt to carbon dioxide and water of which the former is excreted through the lungs and does not give the kidney any work. They also serve to diminish the amount of protein necessary to keep the body in nitrogen equilibrium and spare the body protein when little or no protein is included in the diet. Carbohydrate and fat are therefore the essential constituents of the diet in the first days of acute glomerulonephritis. Every effort should be made to keep the carbohydrate and fat intake as high as feasible. Anorexia nausea and vomiting often interfere with this objective and it may then be necessary to give glucose or fructose by infusion.

4 The water intake must be regulated in accord with the output. During the period of severe oliguria that usually initiates acute glomerulonephritis there is no use in giving large quantities of fluid for it is not excreted and produces edema and hydremia. The fluid intake should balance the urinary volume plus the extrarenal loss of water. This is generally accomplished by a daily fluid allowance of about 1100 cc plus the previous day's urinary volume (cf p 231). To this should be added any volume of water that is lost by vomiting or diarrhea and perhaps 300 cc for each degree Fahrenheit of fever.

Volhard[83] went even further in the principle of saving the kidney from work. He initiated the treatment of acute glomerulonephritis by practically complete *prohibition of food and drink* for a period of from three to five days. At most the patient is given 2 cups of weak tea or a little fruit daily. He believed that this rigorous procedure fulfils a number of indications: it rests the kidney as completely as possible, prevents increase of edema, tends to lower blood pressure and avert convulsive seizures, and diminishes any hydremia that may be present, thereby sparing the heart. Volhard found that patients bear the hunger and thirst very well. For the first few days there is even little complaint of thirst. Lichtwitz[84] also has seen no ill-effects from this seemingly very rigorous procedure and believes it to be the ideal treatment of acute glomerulonephritis. Volhard continued the starvation and thirst until diuresis, diminution in edema and other evidences of improvement set in, up to a maximum of about five days (Lichtwitz has used the procedure for even a week), and then puts the patient on a progressively more liberal diet regulated in accord with the principles outlined above.

I have observed excellent results from Volhard's method of almost absolute starvation and thirst in acute glomerulonephritis. However there was no evidence that these results were superior to those obtained by following the principles detailed above. Many of the patients complained of thirst after a day or two and evidences of dehydration were not rare. Moreover it appeared that weakness was more apt to be pronounced than with a more adequate caloric intake. Theoretically there are objections to the starvation regimen for the protein sparing action of carbohydrate and fat seems highly desirable. And in practice it appears that patients able to take considerable amounts of carbohydrate and fat are both stronger and happier than those kept on Volhard's thirst and starvation regimen and the renal process appears to do quite as well. The starvation treatment probably helps almost entirely through the effects of maximal sodium

Dietary Treatment.—The regulation of the diet forms the cornerstone of the treatment of acute glomerulonephritis. In recent years there has been, in many respects, a complete reversal of the principles formerly followed in the dietotherapy of the disease. In the days when it was believed that obturation of the renal tubules by casts and detritus causes the oliguria, it was customary to give large quantities of fluid in an effort to increase the diuresis and "flush out the kidneys." For this purpose, milk was used, as much as 3000 or 4000 cc. being given daily. But it has been pointed out that this "flushing-out" treatment usually does not fulfil its purpose in acute glomerulonephritis. The urinary volume is not increased and the large amount of fluid ingested serves only to increase the edema and sometimes to produce hydremia that increases the work of the heart. That such hydremia actually occurs is shown by the observation of Siebeck,[47] that when large amounts of fluid are given to such patients there is abnormally great and protracted dilution of the blood. It was during the popularity of treatment with large amounts of fluid that enormous degrees of edema were seen, a manifestation that rarely occurs in a properly managed case of acute glomerulonephritis.

The use of large quantities of milk in acute glomerulonephritis seems ill advised from at least four standpoints.

1. As just mentioned, if the urinary volume is not correspondingly increased—and in the acute stage it generally is not—edema increases and transitory hydremia may be produced with resultant elevation of the cardiac load.

2. Three liters of milk contain almost 5 grams of sodium chloride, which aids in the retention of fluid.

3. Milk is rich in protein (30 grams per liter), a very strong objection in a disease in which renal insufficiency may supervene at any time.

4. In acute glomerulonephritis the glomerular loops are largely blocked (page 549) and the blood does not flow through them. It is difficult to see how ingestion of fluid can cause diuresis from glomeruli whose capillaries are impermeable to blood.

For these reasons, the ingestion of large quantities of milk or other fluids in the early stages of glomerulonephritis seems irrational and is undoubtedly a method of treatment that has done great harm in the past.

The diet in acute glomerulonephritis should be that which makes as little call as possible on the excretory and homeostatic functions of the kidney. The diet will minimize (1) retention of potential urinary constituents and (2) alterations in the composition of the extracellular fluid consequent on intake of food which are kept small by normally functioning kidneys but are augmented when these organs are diseased. It may also be thought that lessening the work of the kidney favors healing, but this is hypothetical. Such a diet may be devised in accord with the following principles.

1. Protein should be restricted at the onset of the disease, for the end products are almost entirely excreted by the kidneys. In the first week of the disease the patient does not have hypoproteinemia. If after this plasma protein deficit develops, the protein content of the diet must be increased.

2. Sodium chloride is likewise excreted almost altogether by the kidneys. The hydropigenic action of sodium is a fundamental disadvantage. The diet should, therefore, be salt poor.

a result of vomiting sodium chloride infusions are to be avoided because of the tendency to edema and hypertension. During the intravenous infusion the patient is to be watched carefully for evidences of cardiac strain (dyspnea, tachycardia, gallop rhythm) or pulmonary edema. If the cervical veins become distended, the infusion should be discontinued. Apart from patients who are dehydrated by vomiting or diarrhea it would hardly seem wise in acute glomerulonephritis to give more than a liter of fluid by vein within any twelve-hour period. In the presence of marked hypertension one should be especially cautious in the administration of fluid by the intravenous route. If there is heart failure, intravenous infusion is contraindicated because of the great danger of pulmonary edema. I have witnessed the precipitation of pulmonary edema during intravenous infusion in acute glomerulonephritis. It has seemed to the writer that intravenous infusions are used more often than necessary in recent years in acute glomerulonephritis. If the patient can take the fluid by mouth there is no call for the intravenous route.

The use of injections of hypertonic or isotonic solutions in the treatment of hypertensive encephalopathy and uremia is discussed in the chapters on these manifestations.

Blood transfusion is indicated in acute glomerulonephritis only for the treatment of anemia.

Sulfonamides and Antibiotics.—When sulfonamides and penicillin were introduced high hopes were entertained that they would be of value in the treatment of acute glomerulonephritis. It was hoped that they would help through eradicating foci of infection in the throat or elsewhere, which many believed to be responsible for persistence and chronicity of glomerulonephritis. While Moncrieff[69] and Suchecki[70] reported soon after the introduction of penicillin that this antibiotic is of value in acute glomerulonephritis, the early hopes have not been fulfilled. There seems to be no good evidence that sulfonamides or penicillin affect the renal process. Nowadays most patients with acute glomerulonephritis are given penicillin but no definite improvement in the disease can be attributed to the antibiotic. This appears to be true even in those cases in which the causative sore throat is still definitely an active streptococcic infection which is cleared up by penicillin. Nor have I seen any beneficial effect on glomerulonephritis from aureomycin, chloromycetin or terramycin. Rapoport[71] *et al.* found no significant differences in the course of acute glomerulonephritis between 33 patients treated with sulfonamides and 40 controls who did not get these drugs. Penicillin or another antibiotic should be used for the treatment of infection present in a patient with acute glomerulonephritis but not with the expectation of influencing the renal lesion. The above-mentioned antibiotics should perhaps be given preference to even highly soluble sulfonamides for fear of nephrotoxic action in an already diseased kidney, although the writer has not seen renal damage due to sulfonamides in acute glomerulonephritis. It should be remembered that with hyposthenuria, while the danger of crystallization of sulfonamides in the tubules is eliminated, high blood levels are quickly attained and persist (*cf.* Fishberg).[72]

restriction on edema, hypertension and heart failure, and these can be obtained quite as well with a salt-poor diet containing considerable quantities of carbohydrate and fat. I have therefore abandoned the starvation regimen except for a day or two in rare cases with pulmonary edema or repeated convulsions due to hypertensive encephalopathy.

The general plan of treatment may be as follows in a case of acute glomerulonephritis starting with marked oliguria and seen at the onset. For the first three or four days the daily fluid intake is about 1100 cc more than the previous day's urinary volume (plus allowance for vomiting, diarrhea and fever), no salt is allowed, and the patient is given liberal quantities of carbohydrates and fats. Among the foods that may be used are fruit, sugar, honey, jellies, rice, salt-poor prepared cereals (Cream of Wheat, Farina, etc.), potato, tapioca, cornstarch, protein-poor vegetables, butter, cream and olive oil, and such fluids as fruit juice, coffee, tea, ginger ale and other sweet drinks to the limit of the fluid allowance. After the first few days, unless there is azotemia, enough protein to maintain nitrogen balance (page 226) is added in the form of salt-poor bread, meat and eggs. Dialyzed milk may be useful but is dear. If there is nitrogen retention, protein restriction is continued. In the presence of extreme oliguria or anuria, the considerable potassium content of vegetables and of orange and grapefruit juices should be borne in mind.

As the patient improves, the diet is made more and more liberal, but until the urine has become normal the protein should not greatly exceed the amount necessary to maintain nitrogen equilibrium and the salt intake should be restricted to about 5 grams daily. After the hypertension and edema have vanished and the protein and formed elements have disappeared from the urine I can see no object in prolonging dietary restriction. Nor can I see any advantage in restricting the diet of those patients who have recovered completely except for a slight trace of protein or a few red cells that persist in the urine for months or years. Of course such individuals should avoid dietary as well as other sorts of excesses, though I know of no actual case of this nature in which a relapse could be traced to rash indulgence in food or drink.

If the patient fails to improve after the initial period, the diet must be regulated according to the manifestations present. Edema calls for salt restriction, while renal insufficiency with its threat of uremia requires that the protein content of the diet be diminished and the fluid intake increased so as to compensate for the diminished concentrating power of the kidney. In the later stages of acute glomerulonephritis, after the initial oliguria has passed, increasing the fluid intake may raise the urinary volume, but if it does not, care should be taken not to embarrass the heart and produce edema by excessive intake of fluid which is not excreted.

Intravenous Infusions.—In patients who because of vomiting or for other reasons are unable to take adequate volumes of fluid by mouth, the intravenous drip may avert dehydration and increase the urinary output. Usually, 5 per cent dextrose solution given at a rate of 30 or 40 drops per minute is the most useful. Recently I have been using the 10 per cent fructose solution which has become commercially available; more energy is obtained from the same fluid volume. Unless there is salt depletion as

noses Following the operations he observed improvement which he attributed to the relief of tension resulting from the splitting of the renal capsule The operation was popularized by Edebohls [a] and since then there has been a considerable number of reports particularly in the surgical literature of cases of very severe acute glomerulonephritis in which rapid improvement has followed decapsulation However in at least a majority of these cases it is not clear that the improvement is actually attributable to the operation and there have also been numerous reports of complete failure

If the operation really does good it cannot be due entirely to the relief of strangulation of a swollen kidney in the unyielding capsule for Volhard has seen success where the kidney was not swollen Kuemmel [77] who has reported excellent results believes them to be due to the removal of the sympathetic plexuses around the renal artery that is carried out in decapsulation i e a periarterial sympathectomy of the renal artery That decapsulation does aid the circulation through the kidney is indicated by the experiments of Huelse and Latzner [78] who found that decapsulation increases the circulation through the kidney of the dog

Volhard believed that the operation should be performed when complete or nearly complete anuria has persisted for three days which is rare in acute glomerulonephritis In the few cases that I have seen in which decapsulation was performed for nephritic anuria there was no notable effect In one instance of acute glomerulonephritis in which decapsulation was performed after five days of anuria the patient passed 75 cc of urine four days after the operation but the relation of the operation to even this minimal success seemed questionable The writer has since seen no evidence that decapsulation actually helps in acute glomerulonephritis and has not advised the operation in a number of years

Caudal Anesthesia —Because caudal anesthesia has been used to reduce the blood pressure in the hypertension of eclampsia gravidarum Hughes [79] and his associates employed it in four patients with hypertension due to acute glomerulonephritis They were able to produce repeated transitory reductions in blood pressure by this measure

Tonsillectomy —The question of tonsillectomy in acute glomerulonephritis arises very often If careful examination reveals no evidence of disease there is no reason for advising tonsillectomy But even if the tonsils are definitely diseased and the glomerulonephritis followed an attack of tonsillitis *tonsillectomy should not be carried out during the acute stage of glomerulonephritis* When the operation is performed at this period there is often marked increase in hematuria and sometimes in other symptoms Tonsillectomy should be postponed until two or three months after the patient has recovered or until improvement has become very slow or stopped Even in such cases the possibility of some exacerbation notably of hematuria must be borne in mind In glomerulonephritis contrary to focal nephritis (see page 661) one rarely sees marked benefit unequivocally attributable to tonsillectomy In fact Illingworth [80] saw no benefit from tonsillectomy in 119 patients in whom the operation was performed during the acute stage of the disease there was no indication that tonsillectomy checked the progress of the disease and reexamination one to twelve years

Cortisone and ACTH —In view of the remarkable effect of these hormones in rheumatic fever there seemed reason to anticipate that they would also be of value in acute glomerulonephritis So far, these hopes have not been attained to any notable extent Farnsworth[73] reported on three children with acute and subacute glomerulonephritis treated with ACTH There was a favorable effect on hematuria, azotemia and hypertension Contrariwise Heller *et al* [83] did not find that cortisone affects the proteinuria or hematuria of acute and subacute glomerulonephritis in any consistent fashion The writer has seen improvement in urinary findings that seemed to be correlated with the administration of these hormones in some cases but the effect did not long outlast the medication and in some patients ceased while the hormone was still being administered More often, there is no effect and sometimes urinary findings and hypertension become aggravated with the administration of the hormone There does not seem to be good evidence that these hormones alter the natural history of the disease and from what is now known their administration does not appear indicated During hormonal administration salt restriction should be rigorous

Antihistamine Drugs —In view of the role of allergic mechanisms in the pathogenesis of acute glomerulonephritis one might anticipate that antihistamines would be of value This does not seem to be the case The writer has used pyribenzamine and other antihistamine drugs in acute nephritis without benefit Lawson[4] gave pyranisamine malleate to alternate patients in a series of 33 cases of acute glomerulonephritis The patients given the antihistamine drug were consistently slightly slower in recovering

Diuretics —Almost all the known diuretics have been tried in acute glomerulonephritis The purine bodies notably diuretin and aminophyllin were the most widely used As a rule they do not increase the urinary output and seem to be valueless Mercurial diuretics rarely produce appreciable diuresis during the oliguric stage of acute glomerulonephritis Indeed they may be followed by decrease in urinary volume and by increase in hematuria While mercurials are ordinarily innocuous to the renal epithelia this may not be true in acute glomerulonephritis For these reasons I do not use mercurials in acute glomerulonephritis I twice saw death from mercurial colitis as a result of the use of the now obsolete novasurol in patients with impaired renal function Ammonium and calcium chlorides are inefficient in acute glomerulonephritis and moreover may produce severe acidosis if renal function is poor Hypertonic *sucrose* solution (100 cc of a 50 per cent solution by vein) sometimes produces profuse diuresis in acute glomerulonephritis as was seen several times when it was given for edema of the brain However I have several times observed that it may fail when the oliguria is very severe and in view of the possible tubular damage (page 361) no longer use it

Dialysis —The use of the artificial kidney and other methods of dialysis of the blood is discussed on page 237

Surgical Treatment —Decapsulation of the kidney in patients with glomerulonephritis was first carried out by Harrison[5] who operated on 2 cases of acute and 1 of subacute glomerulonephritis under mistaken diag

noses Following the operations he observed improvement which he attributed to the relief of tension resulting from the splitting of the renal capsule The operation was popularized by Edebohls[76] and since then there has been a considerable number of reports, particularly in the surgical literature of cases of very severe acute glomerulonephritis in which rapid improvement has followed decapsulation However in at least a majority of these cases it is not clear that the improvement is actually attributable to the operation, and there have also been numerous reports of complete failure

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later showed no evidence that the children with acute glomerulonephritis who had had their tonsils removed fared better than those who still had them. If the operation is performed, penicillin should be given.

What has been said about tonsillectomy also applies, in general, to the surgical treatment of sinus infections. The latter is rarely called for since antibiotics have been available.

Physiotherapy.—Eppinger[81] reported excellent results in acute glomerulonephritis from diathermy of the renal region. He saw almost immediate diuresis in two patients with extreme oliguria. In the only two cases in which I have seen diathermy used the results were entirely negative. Roentgen irradiation of the kidneys has also been recommended (see Salvioli[8]); it has had no effect in the few instances I have seen it used.

Treatment of Individual Manifestations.—The heart and blood pressure must be carefully watched throughout the course of acute glomerulonephritis. Whenever there is evidence of cardiac insufficiency, digitalis should be given. Hypertension is not a contraindication to digitalis. In acute left ventricular failure with massive pulmonary edema, the patient should be propped up, morphine given and tourniquets applied to the extremities so as to trap blood in them. Lanatoside C (Cedilanid) is then given intravenously to the previously undigitalized adult in dosage of 1 to 1.5 mg. In patients who have not been digitalized 0.3 mg. of crystalline strophanthin may be given intravenously; it is highly praised by Continental clinicians but I have seen no advantages over lanatoside C and it is perhaps not as safe. If the arterial pressure falls, caffein may help. However, the most effective measure in acute myocardial failure with pulmonary edema is generally *venesection*. As much as 500 cc. may be taken from vigorous adults and proportionate amounts from children. Smaller quantities, as 200 cc., should be removed from individuals who have been debilitated by preceding illness. Needless to add, in the presence of cardiac insufficiency one should never fail to look for pleural or other serous effusions and remove them if present.

Pains in the kidney region may be alleviated by hot applications, belladonna or mustard plasters; codein may be required.

The treatment of uremia, edema and hypertensive encephalopathy is discussed in the respective chapters.

Duration of Bed rest.—The patient is to be kept in bed until edema and hypertension have disappeared, renal function has returned to normal and the urine has become free of protein and formed elements, even though this takes several weeks. Hyposthenuria often lasts for months without being indicative of chronic disease and does not call for prolongation of bed rest. There are cases (see above) in which either slight proteinuria or microscopic hematuria persists indefinitely after the patient is apparently well in all other respects. If examined a year or two later, such patients usually have normal urine but some go on to the gradual development of chronic glomerulonephritis. In some patients proteinuria persists for a decade or more with no other evidence of disease. Included in this group are those cases which have no proteinuria while in bed but develop it in the erect posture. There seems to be no good end attained by keeping these patients in bed more than a week or two after they are left with only such residual

manifestations The patient with persistent signs (urinary changes, impairment of renal function slight edema hypertension) may be permitted to leave bed when the condition has ceased to improve further for several weeks They should then be allowed to get up but should be very careful about exposure to inclement weather or respiratory infections and should be reexamined frequently Not uncommonly diuresis is diminished for a few days after leaving bed but then the urinary volume returns to its former level

If the patient with residual manifestations of acute glomerulonephritis can afford it it may be well for him to go for several months during the winter to a warm and dry climate

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Chapter

21

CHRONIC GLOMERULONEPHRITIS

In the preceding chapters it has been seen that while many patients with acute glomerulonephritis recover completely and a few die during the acute stage in a certain number the disease persists According to the duration of the process such persistent cases are known to the clinician as subacute subchronic or chronic glomerulonephritis and to the pathologist as the large white kidney or the secondary contracted kidney However each of these represents merely a stage of the same process—links in a continuous chain that begins with acute glomerulitis and may extend through decades to the tiny secondary contracted kidney—and we shall collectively term all of them chronic glomerulonephritis

The pathogenetic unity of the variegated clinical and anatomical pictures of chronic glomerulonephritis has been recognized only within recent years Formerly those cases of chronic glomerulonephritis in which edema is the outstanding feature were grouped with chronic nephrosis under the name of chronic parenchymatous nephritis On the other hand the glomerulonephritides which are dominated clinically by cardiovascular phenomena were not differentiated from essential hypertension the term chronic interstitial nephritis being applied to both The anatomical picture of chronic glomerulonephritis is however distinctive and the large majority of cases can be diagnosed clinically

Ellis s Type 1 and Type 2 Nephritis — Longcope[1] and his associates pointed out that glomerulonephritis may assume two more or less distinct forms The earliest stages of what they termed type A have the clinical picture here described under the designation of acute glomerulonephritis follow an acute infection and terminate in recovery in a high proportion of the cases Type B is usually insidious in onset is not preceded by an obvious acute infection though there is usually some chronic indolent infection of the tonsils or sinuses runs a chronic course dominated by edema and progresses to a fatal termination

Similarly on the basis of extensive clinical and post mortem observations Ellis[2] has differentiated two types of what is called glomerulonephritis by most recent clinicians and in this book He believes these to be two different disorders which he designates as type 1 nephritis and type 2 nephritis Ellis differentiates the two disorders as follows

In type 1 nephritis the onset is usually abrupt and accompanied by such general symptoms as malaise vomiting and headache Hematuria is present at the onset there is a history of antecedent infection in 84 per cent edema is of short duration 60 per cent of the cases occur in the first

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The relations of pregnancy to chronic glomerulonephritis are considered in Chapter 32

The severity of the acute attack is by no means a reliable index of the likelihood of chronicity for chronic disease may evolve from very mild initial attacks Leaving bed too early during subsidence of the acute attack has been regarded as favoring chronicity but this is not proved The question of the relation of persistence of the original infectious focus to development of chronic disease will be discussed below

While there are many cases of chronic glomerulonephritis in which the evolution from the acute stage occurs under our eyes or can be traced with fair certainty from the history there is also a large contingent in which no history of the acute attack can be obtained We see the patient for the first time when he already has an obviously chronic glomerulonephritis and does not recall any symptoms which would indicate previous renal disease In such cases it is probable that the acute attack was so mild that it never came to the attention of the patient The initial renal injury may have followed a sore throat which was considered merely an insignificant cold for which a physician was not consulted Possibly also some of the cases date from scarlet fever in childhood The situation is closely analogous to that encountered in many cases of mitral stenosis which we know have evolved from an antecedent rheumatic infection even though there is absolutely no history of the latter As is the case with chronic valvular disease the cryptogenic cases of chronic glomerulonephritis are more common in adults than in children in the latter a history of the initial attack can be obtained in a high proportion of the cases On the other hand such a history is obtainable in only a minority of adults with chronic glomerulonephritis

Chronic glomerulonephritis occurs at all ages but it is predominantly a disease of the earlier periods of life This is illustrated in the following table of 54 cases of chronic glomerulonephritis which came to necropsy at the Mount Sinai and Montefiore Hospitals

Age at death yrs	*No of cases*
1 to 10	7
11 to 20	11
21 to 30	15
31 to 40	[illegible]
41 to 50	9
51 to 60	2
61 to 70	1
Over 70	0

Almost one half of the cases terminated in the second and third decades

PATHOGENESIS OF CHRONIC GLOMERULONEPHRITIS

It is not definitely known why certain cases of acute glomerulonephritis become chronic while others heal completely In most infectious diseases chronicity is the result of the persistence of the etiologic organism in the lesions But we have seen that the lesions of acute glomerulonephritis do

two decades, and 82 per cent recover. The histological changes described by Ellis are those here presented as the lesions of acute and chronic glomerulonephritis. Ellis stresses that in the cases which die early the glomerular lesion is diffuse and necrosis of the afferent arterioles may be prominent, while in the later stages there are superadded focal changes secondary to lesions of the arteries which may go on to fibrosis.

In type 2 nephritis the onset is insidious without the general symptoms observed in type 1. Hematuria is absent or slight; a history of previous infection is obtained in less than 5 per cent; edema is persistent and the dominant feature; the incidence is similar in all decades, and less than 5 per cent recover. There were no histological observations on cases dying in less than a month after the known onset. Those succumbing during the first months revealed the changes here described as those of chronic (lipoid) nephrosis. With longer duration, there was proliferative glomerulitis going on to hyalinization which affected both the capillary basement membrane and the intercapillary stroma. Lesions secondary to changes in the renal arteries are rarely seen. The fibrosis that develops is diffuse.

To the writer it appears that Ellis's type 1 nephritis represents those cases of glomerulonephritis which are still in the initial acute stage or in which the latter is recognizable in the history. Type 2 nephritis seems to include both cases of chronic (lipoid) nephrosis and of glomerulonephritis in which the acute stage went unrecognized—and there are many of the latter. Ellis states that of 145 cases of type 2 nephritis there are "some 12 cases which on both clinical and histological grounds would be called nephrosis by many observers." Ellis does not accept the concept of nephrosis as a separate entity. The reasons why the writer believes that there is an entity of chronic nephrosis distinct from glomerulonephritis are summarized beginning on page 462. There it is pointed out that not only glomerulonephritis but also lipoid nephrosis may go on to glomerular hyalinization with hypertension and renal insufficiency—failure to recognize that this may occur in lipoid nephrosis is one of the reasons why the independent existence of the latter has been denied.

ETIOLOGY AND OCCURRENCE OF CHRONIC GLOMERULONEPHRITIS

The etiology of acute glomerulonephritis from which the chronic form evolves has been discussed (page 529). Chronic glomerulonephritis seems more apt to develop after certain varieties of the acute disease than following others. Thus postscarlatinal glomerulonephritis becomes chronic in only an exceedingly small proportion of the cases. Chronic glomerulonephritis is more likely to evolve when the acute attack follows sore throat. Most of the cases of diffuse glomerulonephritis occurring in subacute bacterial endocarditis reach the chronic stage if the patient lives long enough. According to the descriptions of Osler, Nobécourt and others (page 535), and my own experience, glomerulonephritis complicating the erythema group of diseases is quite likely to become chronic. Evidence was quoted in the preceding chapter that acute glomerulonephritis in older individuals is decidedly more apt to become chronic than in the young

The relations of pregnancy to chronic glomerulonephritis are considered in Chapter 52

The severity of the acute attack is by no means a reliable index of the likelihood of chronicity for chronic disease may evolve from very mild initial attacks Leaving bed too early during subsidence of the acute attack has been regarded as favoring chronicity but this is not proved The question of the relation of persistence of the original infectious focus to development of chronic disease will be discussed below

While there are many cases of chronic glomerulonephritis in which the evolution from the acute stage occurs under our eyes or can be traced with fair certainty from the history there is also a large contingent in which no history of the acute attack can be obtained We see the patient for the first time when he already has an obviously chronic glomerulonephritis and does not recall any symptoms which would indicate previous renal disease In such cases it is probable that the acute attack was so mild that it never came to the attention of the patient The initial renal injury may have followed a sore throat which was considered merely an insignificant cold for which a physician was not consulted Possibly also some of the cases date from scarlet fever in childhood The situation is closely analogous to that encountered in many cases of mitral stenosis which we know have evolved from an antecedent rheumatic infection even though there is absolutely no history of the latter As is the case with chronic valvular disease the cryptogenic cases of chronic glomerulonephritis are more common in adults than in children in the latter a history of the initial attack can be obtained in a high proportion of the cases On the other hand such a history is obtainable in only a minority of adults with chronic glomerulonephritis

Chronic glomerulonephritis occurs at all ages but it is predominantly a disease of the earlier periods of life This is illustrated in the following table of 54 cases of chronic glomerulonephritis which came to necropsy at the Mount Sinai and Montefiore Hospitals

Age at death yrs	No of cases
1 to 10	7
11 to 20	11
21 to 30	15
31 to 40	9
41 to 50	9
51 to 60	2
61 to 70	1
Over 70	0

Almost one half of the cases terminated in the second and third decades

PATHOGENESIS OF CHRONIC GLOMERULONEPHRITIS

It is not definitely known why certain cases of acute glomerulonephritis become chronic while others heal completely In most infectious diseases chronicity is the result of the persistence of the etiologic organism in the lesions But we have seen that the lesions of acute glomerulonephritis do

not result from the actual invasion of the kidney by bacteria. Some factor other than settling of microorganisms in the kidney must therefore operate to produce chronicity in glomerulonephritis. The nature of this factor, which may be renal or extrarenal, is not definitely established, but several possibilities enter.

1. *Persistence or Exacerbation of the Extrarenal Focus.*—There is much evidence that persistence or exacerbation of the original or another extrarenal infective focus may cause chronicity or exacerbation of chronic glomerulonephritis. Exacerbations of the inflammatory process in this focus (*e. g.*, the tonsils) are accompanied by hematuria or other evidences of lighting up of the glomerulonephritis. The process would thus be analogous to what is so frequently observed in rheumatic valvular disease, in which renewed sore throats are each accompanied by further injury to the already damaged valve. "The patient does not suffer from one attack of nephritis but from one thousand and one," says Emerson,[3] who has observed clinical evidence of the exacerbations. In patients with chronic glomerulonephritis one not uncommonly observes that an intercurrent sore throat results in flaring up of the disease, as manifested by hematuria and impairment of renal function and less often edema or rise in blood pressure.

As Bell and Hartzell[4] point out, anatomical evidence affords strong support for the occurrence of repeated fresh exacerbations in many cases, for one often sees besides old lesions signs of more recent injury. Such a conception explains why so small a proportion of cases of postscarlatinal glomerulonephritis becomes chronic—for here no focus is usually left—while a much greater proportion of the cases that follow tonsillitis results in the chronic disease. But in cases in which glomerulonephritis follows tonsillitis removal of the tonsils does not prevent the progression of the renal process; the general experience here is much the same as in rheumatic valvular disease. Possibly once the kidney has been injured it is more susceptible to injury from any infectious focus in the period before *complete* recovery. This is not true after *total* healing, for then recurrence of glomerulonephritis is an extreme rarity.

Support for the theory that chronicity of glomerulonephritis is a result of persistence of activity in the extrarenal focus of infection is afforded by the observations of Winkenwerder, McLeod and Baker.[1] They found that in cases of glomerulonephritis following hemolytic streptococcal infections the numbers of the organisms diminished during recovery but persisted during progression. They also found that glomerulonephritis complicating an acute infection with systemic reaction was much more apt to terminate in recovery than when the renal mischief complicated a chronic infection.

Further evidence that activity of an infective focus is concerned in some cases of chronic glomerulonephritis has been afforded by observations on exacerbations. Studying 28 exacerbations (marked by increased hematuria and usually by further impairment of renal function) in 13 patients with chronic glomerulonephritis, Seegal *et al.*[5] found that an infection, usually with Group A hemolytic streptococci, preceded the exacerbation by one to four days. Earle[6] and his associates observed rise in the antistreptolysin titer in 24 of 33 exacerbations in chronic glomerulonephritis; in 6 there was no rise and in 3 the data were inconclusive.

2. *Intrinsic Progressiveness of the Glomerular Lesions.*—In many patients glomerulonephritis progresses to renal insufficiency over a period of years during which there is no evidence of infection. There may be no history of a sore throat for years, examination of the upper respiratory tract and sinuses by a specialist is negative and the antistreptolysin titer is not elevated. Accelerated sedimentation of the red cells is not necessarily evidence of infection, for this may result from changes in the plasma proteins consequent on proteinuria. These patients have no acute exacerbations with hematuria but slowly progress without obvious cause over years and decades to renal insufficiency and uremia. In such cases it seems probable that the glomerular lesions produced by the original causative infection may have carried in themselves the seeds of progression. The original proliferative changes in the walls of the glomerular loops and capsules and the thickening of the basement membranes may be so great as gradually to produce ischemic changes terminating in fibrosis and obliteration. The number of glomeruli is greatly diminished in long standing glomerulonephritis.

3. *Development of Arterial and Arteriolar Lesions.*—It will be seen below (page 610) that patients with glomerulonephritis develop *arteriolar sclerosis* and endarteritis obliterans. These may attain a high degree and lead to ischemic atrophy of renal parenchyma. Patients with *chronic glomerulonephritis may* develop very high blood pressure and the clinical picture of malignant hypertension. At necropsy necrotizing arteriolar lesions are found in the kidney. In these cases the sequence of events apparently is that the glomerulonephritis leads to the hypertension, and the latter is correlated with the arteriolar and arterial lesions. Sometimes the arteriolar lesions and their consequences are so prominent that without the history it would not be clear that one is dealing with chronic glomerulonephritis. Arteriolar lesions, when present, contribute to the progression of the renal disease, slowly with arteriolar sclerosis and endarteritis obliterans, fulminantly in the case of arteriolar necrosis.

In those cases of glomerulonephritis occurring predominantly in the young in which progression is marked by repeated hematuric exacerbations and in which there is continuous or intermittent active infection in the throat, it seems likely that persistence of infection is the cause of chronicity. In the slowly progressive cases without evidence of a persistent infective focus, the other factors are presumably predominant. Arteriolar and arterial changes become important especially in the older age groups and where hypertension is pronounced.

PATHOLOGICAL ANATOMY OF CHRONIC GLOMERULONEPHRITIS

The anatomical picture encountered at necropsy varies with the period of time that has elapsed between the acute glomerulonephritis and death, which may be from a few months to several decades. While in the acute phase only the glomeruli are involved notably, the other structures of the kidney soon become implicated so that in older cases there are changes in all the renal elements—glomeruli, tubules, vessels and interstitium. More

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substance The degree of contraction may be extreme so that the weight of both kidneys in an adult is less than 75 grams All sizes between such small organs and the normal are met with In fact there are slightly enlarged granular kidneys evidently where the hypertrophy has more than compensated for the lost parenchyma The granulation is usually fine and fairly evenly distributed However at times the granulations are coarse or both coarse and fine nodules are found in the same organ The granules are usually white or yellowish in color but may be a brownish red The intervening sunken areas are darker in color Small cortical cysts are seen on occasion but are not as common as in the primary contracted kidney

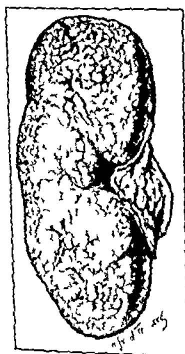


Fig 7 Chronic glomerulonephritis in the stage of secondary contraction uniform granulation of the surface

On section of the kidney which offers increased resistance to the knife it is seen that all parts of the organ are shrunken The cortex is narrowed and irregular so that in places the pyramids may practically *reach the* surface The markings are *obliterated* large portions of the cortical substance being replaced by irregular grayish and yellowish areas of fibrosis and lipoid changes The medullary pyramids are also atrophic and in extreme cases the delimitation of cortex from medulla cannot be made out There may be scattered hemorrhages The vessels are usually notably thickened thus may be quite as marked as *in far advanced* primary contracted kidneys In fact it is far from uncommon that one is unable to

over, as brought out especially by Oliver,* the regressive changes are accompanied by conservative adaptations of both the parenchyma and blood vessels. Thus, exceedingly complicated and variegated pictures are the rule.

Macroscopic Appearance.—*When glomerulonephritis has lasted from a* few months to as much as three or four years, the most frequent finding is the "large white kidney," as it was termed by Wilks,[8] a gross appearance that also occurs in chronic nephrosis. The kidneys are enlarged and their weight may exceed even double the normal, though this is exceptional. The consistency is soft. The capsule strips readily without damage to the kidney substance. The surface is usually pale and of a yellowish or grayish-white color. In the presence of marked congestion, the color is more brownish. Small hemorrhages are found quite frequently and may be very numerous.

On section, the parenchyma swells above the edge of the capsule. The cortex is broadened and the markings obscured; the cortical substance appears moist and shiny, of a color similar to that of the surface. There are often areas of deeper yellow lipoid change. In instances in which the deposition of fat and lipoid in the tubules is very great, the entire section presents a uniform buttery yellow color and greasy feel (myelin kidney of McNee[9]). Some of the glomeruli are enlarged, appearing as grayish, translucent points, others may be hemorrhagic. Hemorrhages may be present as streaks or dots. The medulla is well demarcated from the cortex by its deeper brownish red color.

The picture of the large white kidney just sketched corresponds to the stage of glomerulonephritis in which the changes consist predominantly in inflammatory lesions of the glomeruli and secondary degenerative changes in both glomeruli and tubules. There is then a gradual but radical alteration in the picture as the specific renal elements are completely destroyed and disappear. Their place is taken by connective tissue (replacement fibrosis) which gradually shrinks with resultant contraction of the kidney. The intact glomeruli and much more strikingly their appertaining tubules hypertrophy. Islands of such hypertrophied elements protrude above the surface to constitute the well-known granules. It is thus that from the large, soft, smooth kidney of the earlier stages there develops the small, hard, granular organ long known as the "secondary contracted kidney" because it evolves from a previously enlarged kidney. The time required for this transformation varies. Sometimes well marked contraction and granulation are encountered when the disease has lasted but two or three years, while in other cases there may be little or none after even five years. Evidently the "tempo" of the process varies from one case to another; probably also the number and severity of the acute exacerbations and the degree of arterial change also play parts.

The fully developed secondary contracted kidney is a small, hard, granular organ from which the thickened capsule is removed with some difficulty and often only at the expense of taking along bits of the cortical

* For what is known of the architecture of the kidney in chronic Bright's disease the reader is referred to the pioneer and classic investigations of Oliver,[7] in which he studied individual nephrons isolated by micro-dissection.

Depending on whether or not epithelial proliferation with formation of crescents is a striking feature Fahr[11] Loehlein[14] and others have differentiated two groups of cases of early chronic glomerulonephritis Fahr terms the cases in which the glomerular lesions are confined to the capillary loops with little or no capsular proliferation *intracapillary glomerulonephritis* * while he applies the term *extracapillary glomerulonephritis* when the lesions of the tuft are accompanied by extensive formation of epithelial crescents To indicate that the extracapillary cases present a more severe and rapidly fatal clinical picture than those with only intracapillary lesions Loehlein speaks of stormy and mild types Such a distinction is by no

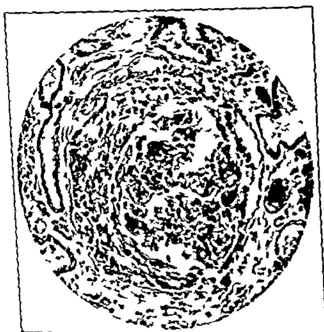


Fig 98 —Malpighian body in subacute glomerulonephritis Proliferation of capsular epithelium resulting in crescent formation also changes in the glomerular tuft

means universally true but in general it seems that extracapillary glomerulonephritis is usually found in cases which have succumbed relatively quickly to renal insufficiency while the cases with largely intracapillary lesions tend to a more protracted course Quite possibly compression of the glomerular tuft which is often obvious in the sections serves to accelerate the onset of renal insufficiency though presumably the intracapillary process is especially severe in cases in which the epithelial reaction is so marked

* Against the word intracapillary it may be objected that there is more or less proliferation of the glomerular epithelium outside the basement membrane of the capillaries (see page 549) MacCallum s criticism of the conception of intracapillary nephritis was mentioned on page 550

decide from the gross appearance whether he is dealing with a primary or a secondary contracted kidney. The pelvic fat is increased in quantity.

Microscopic Picture.—It has been seen (page 548) that in the first stages of glomerulonephritis the changes are confined to the glomerular capillaries. If the disease lasts a longer time, these lesions within the glomerular tuft progress and the other renal structures become implicated. In some cases the capsular epithelium undergoes inflammatory proliferation. The tubules very soon show degenerative changes. In the course of time the lesions of the affected glomeruli and tubules lead to their obliteration and disappearance. Such parenchyma as survives hypertrophies in an effort to compensate for the destroyed elements. The interstitial connective tissue proliferates and occupies the space vacated by the lost parenchyma. The final result, if the patient lives long enough, is the total disorganization of the architecture of the kidney. The particular picture encountered depends on the stage of the progress at which death has occurred. We shall follow individually the progress of the lesions in each of the renal structures.

Malpighian Bodies.—The Malpighian bodies are diffusely involved in the early stages; in fact, in many cases it is impossible to find a glomerulus which appears normal. In many of the glomeruli the same changes as are found in the acute stage are to be seen. The glomerulus is enlarged, due to swelling and proliferation of the capillary endothelium and glomerular epithelium, and the lumens of the capillaries are further blocked by the accumulation of albuminous exudate and leukocytes. Such glomeruli are altogether or almost bloodless. In other glomeruli, however, it is seen that the circulation has been reestablished through at least some of the loops and these are congested with blood. The capsular spaces of many of the glomeruli contain coagulated exudate, fibrin, red blood cells, leukocytes and desquamated epithelia; capsular adhesions are present in places.

In addition to the above changes in the glomerular tuft, there is proliferation of the capsular epithelium in many of the cases which come to necropsy at any time from weeks to years after the onset. This results in the formation of crescentic masses of epithelial cells known as *epithelial crescents*. According to McGregor[10] the inner layers of the crescent are sometimes formed by proliferated and desquamated glomerular epithelium. Such epithelial crescents may have a thickness of several layers of cells, compress the tuft and even proliferate into the mouth of the urinary tubule. Later the cells of the crescents undergo fatty and other degenerative changes, desquamate, and organization by connective tissue from without occurs. (A different interpretation is given by Bell[11] and Allen,[1] who believe the epithelial cells are transformed into fibroblasts and form the fibers.) Sometimes there are numerous spaces within the crescents which communicate with the free part of the capsular space. While the presence of crescents is usually an indication that the glomerulonephritis is of relatively short duration (subacute), they may also be found in older cases, being here presumably the result of comparatively recent acute exacerbations. Thus I saw abundant crescent formation in a case known to have been of over five years duration. A few crescents, usually small, are not uncommon in old secondary contracted kidneys.

are very closely set many being seen in a field, this is due to collapse of the appertaining tubules and shrinkage of the connective tissue which replaces them The appearance is then much like that seen in the hydronephrotic contracted kidney Ultimately however the hyaline remains of the glomeruli are largely absorbed and in old secondary contracted kidneys there are considerable areas in which not even the vestiges of glomeruli can be seen Moritz and Hayman[11] found that in chronic glomerulonephritis from one half to two-thirds of the glomeruli may disappear without leaving traces demonstrable through the microscope

TUBULES —The tubules are involved in all the stages of chronic glomerulonephritis In some instances the tubular lesions are not striking for a

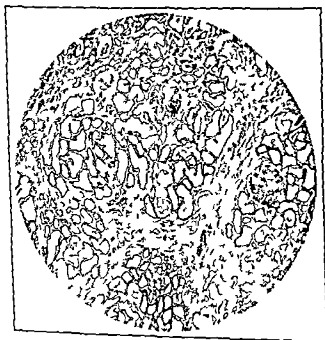


FIG 60 —Chronic glomerulonephritis with renal insufficiency Two hypertrophic glomeruli surrounded by islands of tubules in a state of compensatory hypertrophy and dilatation

considerable period but as a rule they quickly become evident At a very early stage hyaline-droplet and more particularly fatty and lipoidal alteration of the tubular epithelium appears It is usually at its maximum in those cases of some months to a few years duration which macroscopically appear as the large white kidney Much of the lipoid is doubly refractile (cholesterol esters) The fatty and other structural changes are generally most marked and seen first in the proximal convoluted tubules but any part may be affected As a rule the changes are diffuse but occasionally only scattered groups of tubules are involved There is more or less desquamation of tubular epithelia which are found in the lumens together with casts red and white blood cells and cellular detritus Scattered necroses are seen at times but are not prominent

Such of the glomeruli as do not recover from the acute inflammatory process undergo hyaline degeneration The walls of the affected glomerular capillaries together with their contents are converted into hyaline masses in which nuclei become fewer and finally disappear McGregor[10] found that the intracapillary hyaline fibers which she demonstrated in acute glomerulonephritis (see page 551) play an important part in the hyalinization of the glomerulus According to her description as the process advances these hyaline fibers increase in number and thickness and finally fuse with one another and the basement membrane of the capillary Hyaline thickening of the capillary wall (capillary basement membrane?) also contributes The process of hyalinization advances with varying rapidity in different

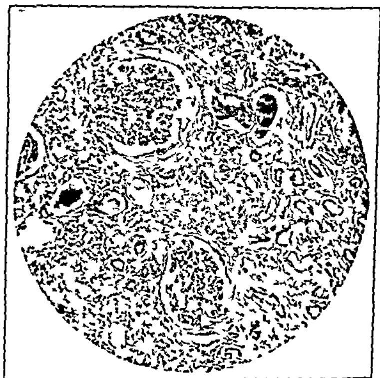


FIG 29 —Chronic glomerulonephritis Two glomeruli showing intracapillary changes with secondary degeneration and atrophy of tubules and replacement fibrosis

capillaries so that small hyaline areas appear in various parts of the glomerulus while the remaining portions are still very rich in nuclei the whole presenting a very characteristic appearance Gradually the hyaline areas fuse the number of nuclei diminishes and finally a homogeneous hyaline sphere remains At the same time the capsule undergoes fibroid transformation as described above The hyaline glomerulus is thus often surrounded by a concentrically laminated ring of connective tissue which ultimately also becomes hyaline and fuses completely with the hyaline glomerulus The hyaline *glomerulus and fibroid capsule can often* be told apart for a long time by the difference in the staining particularly in the Van Gieson preparation At one stage of the process the hyaline glomeruli

urinary volume is greater than normal. The result is that each urinary tubule processes a much larger volume of fluid than normally, and the dilatation (increased tubular capacity) may be the histological expression of the requisite adaptation. Volhard[16] pointed out that animals sacrificed during vigorous diuresis exhibit tubules which are dilated and lined by low epithelium.

The beautiful studies of Oliver[17] and his pupils, in which they isolate and make models of the individual nephrons, show that in chronic glomerulonephritis there persist *aglomerular tubules*, *i.e.*, tubules completely cut off from their appertaining glomeruli by scarring processes. Oliver finds that the aglomerular tubules are nourished by a branch (known as Ludwig's vessel) which leaves the afferent arteriole before it reaches the glomerulus and by passing the latter empties into the peritubular capillaries. Other arterial branches also extend from the interlobular and even larger arteries directly to the network surrounding the tubules. Oliver's investigations reveal that all these arterial vessels which by-pass the glomeruli are rare and functionally insignificant in health, except perhaps in old age, but are newly formed and highly developed in chronic renal disease with glomerular obliteration. Oliver shows that aglomerular tubules may be well preserved and even hypertrophic, and believes that they function. If such is the case, the dominant conceptions of the pathological physiology of the contracted kidney are doubtless in need of revision. However, Cargill[18] found general agreement between the over-all blood flow through the glomeruli and that through the tubules in chronic glomerulonephritis (glomerular blood flow was measured by the excretion and extraction of inulin and tubular blood flow by the excretion and extraction of PAH). These findings do not support the conception of *over-all* dissociation of glomerular and tubular function in chronic glomerulonephritis, but do not disprove such dissociation in individual nephrons. More plausibility is lent to the conception of the functioning of aglomerular tubules in chronic renal disease by the existence of aglomerular kidneys in certain fishes and especially, as pointed out by Oliver, by Grafflin's[19] finding that the daddy sculpin begins life with a glomerular kidney which is then converted into a purely tubular organ by destruction of the tufts.

THE INTERSTITIUM.—From an early stage there is proliferation of the interstitial connective tissue. As the tubules atrophy their place is taken by connective tissue (replacement fibrosis). It is this extensive interstitial fibrosis that led to the old term "chronic interstitial nephritis," but Weigert (see Chapter 13) long ago showed that the interstitial changes are secondary to those in the specific renal elements. The connective tissue contains large numbers of lymphocytes and mononuclear wandering cells. These cells may form dense interstitial infiltrates. Occasionally the infiltrates are periglomerular. Small hemorrhages are often present. When there are extensive degenerative processes in the tubules, deposits of doubly refractile lipoids identical with those occurring in chronic nephrosis (page 449) are found. In the advanced stages large areas of connective tissue separate the isolated islands of functioning parenchyma; in these are the atrophic remnants of tubules and the hyaline vestiges of glomeruli

With complete obliteration of glomeruli, the appertaining tubules gradually atrophy and collapse. They are seen as little groups of epithelial cells in the midst of the large areas of replacement fibrosis which occupy the greater portion of the field in the secondary contracted kidney. Small areas of tubular atrophy are often present in cases of but a few months' duration.

Attempts to regenerate the destroyed tubules become manifest at a relatively early stage. The newly-formed cells are often unusually large and have deeply staining nuclei. Not uncommonly the efforts at regeneration lead to the formation of atypical tubules of irregular shapes. Rarely

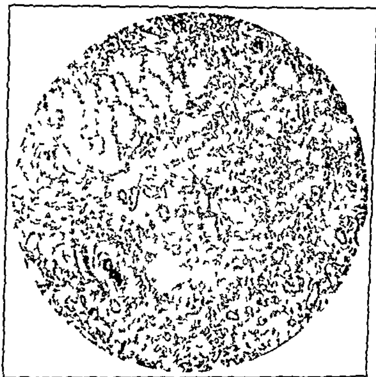


FIG 31 — Chronic glomerulonephritis in stage of secondary contraction. Hyalinized glomeruli, extensive replacement fibrosis and an island of compensatory tubular hypertrophy and dilatation.

giant cells are formed or the regenerative process may lead to the formation of minute adenomata.

In cases in which widespread destruction of renal elements has produced protracted and severe impairment of renal function, there are usually islands of dilated tubules lined by strikingly low, sometimes almost flat, epithelium. The connection of these dilated tubules with hypertrophied glomeruli is generally evident. Such islands often constitute the fine granulations of the surface. It is probable that the dilatation of the surviving tubules is a manifestation of the way in which they function. The number of surviving nephrons in such kidneys appears to be proportionately much more reduced than is the volume of filtration and the ultimate

Various explanations of the origin of endarteritis obliterans in glomerulonephritis have been offered. The fact that the endarteritis is confined to the renal vessels makes it improbable that it is of "toxic" origin. Endarteritis obliterans histologically similar to that of chronic glomerulonephritis is often seen in vessels in the midst of areas of granulation tissue as in tuberculous or chronic pneumonic processes in the lung. While such a mechanism may be an accessory factor in the production of endarteritis in glomerulonephritis, it is not the primary one, for endarteritis is often seen before there has been widespread replacement fibrosis. Nor is the endarteritis the direct result of hypertension alone, for it may occur in cases in which the blood pressure has not been at the very high levels which are accompanied by endarteritis and arteriolar necrosis in the malignant phase of essential hypertension. Volhard[22] believes that the endarteritis in both the kidney and the retina is the result of the angiospasm which he postulates as the cause of the glomerular lesions. It has been seen (page 561), however, that the evidence in favor of the primarily angiospastic nature of glomerulonephritis is not convincing.

It seems more probable that the endarteritis is the consequence of the obstruction to the flow of blood resulting from the blocking of the glomerular capillaries. It is in the cases of glomerulonephritis in which an active inflammatory process has existed in the glomeruli for some time that endarteritis is found. Since the old experiments of Thoma[24] it has been well known that when an artery is ligated, and in the physiological obliteration of such vessels as the umbilical vein, there gradually appears intimal thickening due to connective tissue proliferation without hyperplasia of the internal elastic membrane. These findings are similar to the endarteritis that occurs in chronic glomerulonephritis, and it would seem that the cause of the endarteritis that occurs in this condition is akin to that in ligation experiments, namely, obstruction to the flow of blood.

Hypertrophy of the Muscular Layer.—Hypertrophy of the muscular layer of the arteries was first noted by Johnson[25] and confirmed by the measurements of Ewald.[26] Volhard observed that it is found in glomerulonephritis but not in essential hypertension. I have been able to confirm these observations in a large number of cases except that in some instances of the malignant phase of essential hypertension the media also appears hypertrophic. The muscular hypertrophy is found in cases of glomerulonephritis of several years' duration in which the hypertension has been severe. It is not seen in early cases. Occasionally the arterioles in old secondary contracted kidneys have medial hypertrophy, but in most such cases there is distinct and often marked medial atrophy with the development of arteriolosclerosis. The vessels of the kidney affected are those of all sizes down to and including the interlobular arterioles. I have not found muscular hypertrophy in the arterioles of other organs than the kidney (but see the findings of Kernohan, Anderson and Keith in essential hypertension quoted on page 287). Here again I had no opportunity to study the retina, in which Volhard states that the media of the arterioles is hypertrophic. According to Fischer and Schlayer[27] and Moschcowitz[28] the media of the larger arteries, as the radial, is hypertrophied in chronic glomerulonephritis.

ARTERIOLAR LESIONS.—Arteriolar lesions are prominent features of many instances of chronic glomerulonephritis. Rare in cases of short duration, they become more common the longer the disease lasts, and are a regular finding in long-standing cases. The great frequency of arteriolar lesions in long-standing chronic glomerulonephritis is illustrated by the findings of Horn[20] and his associates, who observed in 49 cases of chronic glomerulonephritis 14 instances of arteriolar sclerosis, 13 of what is here called endarteritis obliterans and 22 of arteriolar necrosis. Four varieties of arteriolar change are encountered in chronic glomerulonephritis:

1. Endarteritis obliterans
2. Muscular hypertrophy
3. Arteriolosclerosis
4. Arteriolar necrosis

Endarteritis Obliterans.—Endarteritis obliterans is present in almost all cases of several years' duration in which active destruction of glomeruli is still in progress. The beginnings of endarteritis obliterans are occasionally seen in cases succumbing within the first year, but it is slight. Also in old secondary contracted kidneys, endarteritis obliterans is sometimes found but is more often absent. The lesion affects the arterial vessels of all sizes in the kidneys. It consists in the variety of diffuse intimal thickening termed "regenerative connective tissue proliferation" by Jores[21] and is identical with the intimal thickening that occurs when a vessel is ligated or in the physiological obliteration of such vessels as the umbilical vein. The thickening results from the proliferation of ordinary (collagenous) connective tissue in the intima of the vessel, the elastic membrane not being hypertrophied and reduplicated as in arteriolosclerosis. If elastic tissue is found in the intima, it is in the form of fine fibrils in the midst of the collagenous fibers, but the basis of the process is the proliferation of collagenous connective tissue. Fatty and hyaline degeneration of the thickened intima is common. The connective-tissue thickening of the intima is often accompanied by endothelial proliferation, and the final result is not uncommonly complete obliteration of the lumen.

It is usually easy to differentiate arteriosclerosis and endarteritis obliterans in vessels of the size of the interlobular arteries of the kidneys or larger. In such vessels the hyperplasia of the internal elastic lamina in arteriosclerosis is striking. The differentiation is sometimes more difficult or impossible in the case of the vasa afferentia near their entrance into the glomeruli. In these arteriolosclerosis is usually manifested solely by the subendothelial deposition of hyaline substance, and precisely the same appearance can be produced in endarteritis obliterans of these minute vessels by hyaline degeneration of the proliferated connective tissue of the intima. Fatty change may occur in either variety of intimal thickening. In cases of considerable duration endarteritis obliterans, arteriosclerosis and arteriolosclerosis may all be seen in the same kidney.

Endarteritis obliterans did not occur in the vessels of other organs than the kidney in a series of cases of glomerulonephritis which I[22] examined. However, I did not study the retina, in which endarteritic changes are generally present when there is hypertensive neuroretinopathy.

are of the opinion that the arterial obliteration is of great importance in production of atrophy of the kidney in chronic glomerulonephritis. It seems probable therefore that arteriolosclerosis resulting from the hypertension is partially responsible for the final renal failure in many patients with secondary contracted kidney who die of uremia after many years of hypertension with relatively intact renal function. The arteriolosclerosis adds the *coup de grace*, so to speak, to the damage already wrought by the nephritic process.

Arteriolar Necrosis.—This lesion occurs under two circumstances. What seems to be a necrotizing arteriolitis of at least partially inflammatory origin (though the mechanical factor of hypertension may also play a part) and identical with that found in acute glomerulonephritis (page 602) occurs in some of the cases that die within the first year. It is also found on rare occasions when chronic glomerulonephritis of longer standing is terminated by an acute exacerbation. The arteriolar necrosis may be accompanied by necrosis of glomerular loops.

Arteriolar necrosis in the kidneys and to a much less extent in other organs sometimes also develops in chronic glomerulonephritis in which the diastolic pressure has been very high for a protracted period. This form of arteriolar necrosis would seem to be a direct consequence of the extremely high blood pressure and of the same pathogenesis as the arteriolar necrosis in the malignant phase of essential hypertension (page 683). It would appear probable that the necrosis of the renal arterioles causes further acute and severe impairment of the already damaged renal function and thus contributes significantly to the production of the final renal failure. The clinical picture is then practically identical with that seen in the malignant phase of essential hypertension and may be termed the malignant phase of glomerulonephritis. (See page 826 for the clinical picture associated with arteriolar necrosis.)

CLINICAL PICTURE OF CHRONIC GLOMERULONEPHRITIS

Chronic glomerulonephritis presents a great variety of clinical pictures so dissimilar that the older clinicians considered them as distinct diseases. There are almost monosymptomatic forms in which a single symptom completely dominates the clinical course as well as polysymptomatic cases in which variegated manifestations are blended to constitute an exceedingly complex clinical picture. Before proceeding to the analysis of the individual symptoms some of the clinical types of chronic glomerulonephritis may be outlined briefly.

Severe or Subacute Type.—There are cases in which the urinary abnormalities, hypertension, edema, impairment of renal function, and other manifestations of the acute stage do not abate and, in fact, are intensified so that death from uremia results within a few months.

Nephrotic Type.—Edema may be the dominant manifestation for months and years in the absence of impairment of renal function, hypertension and hematuria—the so-called nephrotic type of glomerulonephritis. During this period, if there is no history of the acute onset, differentiation from

Arteriolosclerosis — Arteriolosclerosis is present in practically all cases of chronic glomerulonephritis in which there has been arterial hypertension for many years. The lesions are identical in histology and distribution with those found in essential hypertension and have been discussed on page 284.

The consequences of the arteriolar lesions for the renal parenchyma are of interest. Severe arteriolosclerosis in chronic glomerulonephritis must injure the kidney much as it does in essential hypertension. Volhard believes that endarteritis obliterans is responsible for the progression of many cases of chronic glomerulonephritis. However, endarteritis is probably of only secondary importance in this direction for the affected vessels

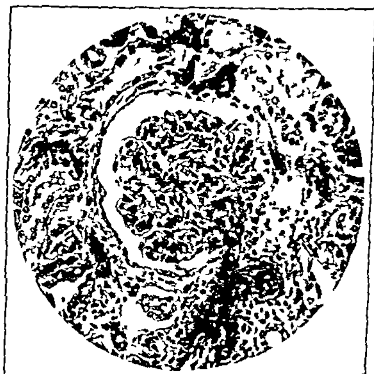


Fig. 32 — Arteriolar necrosis of vas afferens in subacute glomerulonephritis. The vas afferens is converted into a necrotic mass (dark in the picture) with cellular infiltration about it.

are those which lead to glomeruli that have previously been functionally impaired. Arteriolosclerosis on the contrary may affect vessels supplying intact glomeruli and destroy them by cutting off the blood supply, precisely as occurs in essential hypertension. The striking narrowing of the arterial tree of the kidney in chronic glomerulonephritis has been clearly brought out by the studies of Baehr and Ritter,[9] who injected the branches of the renal artery with a radio opaque mixture and made roentgen ray photographs of the organ. They found that in such preparations the withered and bare appearance of the arterial tree described by Gross[30] in contracted kidneys applies quite as well to the terminal phases of chronic glomerulonephritis as to the primary contracted kidney. Baehr and Ritter

is closely akin to the usual picture of the malignant phase of essential hypertension (Chapter 26) Dr George Baehr has long emphasized the analogy After following one or another of the courses just described for a varying number of years the arterial pressure mounts to much higher levels than had previously been maintained Especially important is the rise in the diastolic pressure After the diastolic pressure rises to levels which in most readings exceeds 120 mm for a period of from a few months to a year or two papilledema generally develops With this or soon after headache and perhaps convulsions or other symptoms of increased intracranial pressure appear and are joined by rapidly progressive impairment of renal function which leads to uremia Necropsy often discloses in addition to the usual findings in chronic glomerulonephritis arteriolar necrosis like that found in the malignant phase of essential hypertension The entire picture simulates that of the malignant phase of essential hypertension both in the latter and in glomerulonephritis the diastolic pressure has risen to levels so high that it causes acute damage to the renal arterioles retinopathy and perhaps edema of the brain (see page 823)

Onset —At times chronic glomerulonephritis evolves under observation from the acute stage or there is a definite history of the latter This is usually true in children but in adults a majority of the cases are first seen when they are evidently already of considerable standing and more often than not no history of an acute attack can be obtained There are cases of chronic glomerulonephritis in which the onset and the sore throat or other infection preceding it seem typically those of acute glomerulonephritis and only a history of a previous attack or the presence of marked cardiac hypertrophy make it probable that the present incident is an exacerbation of an old process Rarely necropsy first reveals that what was regarded clinically as acute glomerulonephritis was actually chronic

Apart from the cases which start with the picture of acute glomerulonephritis various symptoms may bring the patient with the chronic disease to the doctor Among the common initial manifestations are headache vertigo swelling of the face or feet weakness pallor anorexia emaciation nocturia polyuria epistaxis and shortness of breath The very first symptoms may be of uremic origin as nausea vomiting headache mental torpor somnolence disorientation pruritis or twitching The initial examination then reveals marked nitrogen retention in the blood Occasionally the patient goes first to a stomach specialist because of the onset with gastric symptoms On unusual occasions convulsions or other manifestations of hypertensive encephalopathy are the first indication of the disease Rarely the first symptom is impairment of vision from hypertensive retinal lesions which leads the patient to consult an ophthalmologist

Nowadays it is common for glomerulonephritis to be revealed first by proteinuria or hypertension discovered in an insurance or periodic physical examination

Edema —While edema is an important and even dominant feature in many instances of chronic glomerulonephritis it is to be emphasized that in other cases edema is absent throughout the course of the disease Edema is usually greatest in the first months or years of chronic glomerulonephritis if the patient lives longer the edema almost always clears up completely or

chronic nephrosis may be impossible Ultimately, however, impairment of renal function and hypertension appear, while the edema often regresses or disappears completely Even this course of events may also occur in chronic nephrosis as the glomeruli become hyalinized (page 465) A not uncommon sequence of events is for the edematous stage to be followed by a variable period which may amount to many years in which proteinuria is the only abnormality until finally hypertension and impairment of renal function make their appearance—usually the final act in the drama Anatomically, these cases have passed from the stage of acute glomerulo nephritis through that of the large white kidney to the secondary contracted kidney

Hypertensive Type —Other patients emerge from the acute stage with little more than arterial hypertension Edema may have been but slight or even totally absent and the urinary abnormalities consist in only modest proteinuria and cylindruria For a long time even many years the clinical course is akin to that of essential hypertension in fact in older people with no history of the acute attack the clinical differentiation of chronic glomerulonephritis from essential hypertension may be impossible For years the patient may feel well despite the hypertension Eventually however, though it may be only after many years impairment of renal function appears and the end is then usually not far off Sometimes though this is uncommon cardiac failure or cerebral hemorrhage terminate the disease while renal function is still intact

Recurrent Type —The patient may have repeated acute attacks with hematuria edema and hypertension At first he remains with only proteinuria after the exacerbation has subsided Finally however persistent hypertension and impairment of renal function appear and progress A classical example of such a case was reported by Mann[19] who followed the patient over a period of twenty-eight years until he died with contracted kidneys For the first seven or eight years after the original seizure the patient had occasional acute attacks with bloody urine they usually followed exposure to cold Proteinuria was always present After this the heart began to hypertrophy the specific gravity of the urine gradually fell polyuria appeared and the patient died of uremia Such an outspokenly recurrent course is unusual but less obvious acute recurrences are very common

Latent Type —Following acute glomerulonephritis the patient may remain with no demonstrable abnormality other than proteinuria which may be but slight The proteinuria may be unaccompanied by other symptoms for many years not uncommonly it is accidentally discovered in an insurance or other routine examination and there is no history of an acute attack Such cases in which only proteinuria remains after the acute attack are known to the Germans as *Heilung mit Defekt* (healing with a defect) Some such instances seem to last for decades without any harm to the patient or very rarely eventually clear up Others on the contrary ultimately develop the typical picture of chronic glomerulonephritis with hypertension and impaired renal function

The "Malignant Phase" of Chronic Glomerulonephritis —In some cases of chronic glomerulonephritis a sequence of events occurs which

is closely akin to the usual picture of the malignant phase of essential hypertension (Chapter 26). Dr. George Baehr has long emphasized the analogy. After following one or another of the courses just described for a varying number of years, the arterial pressure mounts to much higher levels than had previously been maintained. Especially important is the rise in the diastolic pressure. After the diastolic pressure rises to levels which in most readings exceeds 120 mm. for a period of from a few months to a year or two, papilledema generally develops. With this or soon after, headache and perhaps convulsions or other symptoms of increased intracranial pressure appear, and are joined by rapidly progressive impairment of renal function which leads to uremia. Necropsy often discloses, in addition to the usual findings in chronic glomerulonephritis, arteriolar necrosis like that found in the malignant phase of essential hypertension. The entire picture simulates that of the malignant phase of essential hypertension; both in the latter and in glomerulonephritis, the diastolic pressure has risen to levels so high that it causes acute damage to the renal arterioles, retinopathy, and perhaps edema of the brain (see page 823).

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Apart from the cases which start with the picture of acute glomerulonephritis, various symptoms may bring the patient with the chronic disease to the doctor. Among the common initial manifestations are headache, vertigo, swelling of the face or feet, weakness, pallor, anorexia, emaciation, nocturia, polyuria, epistaxis, and shortness of breath. The very first symptoms may be of uremic origin, as nausea, vomiting, headache, mental torpor, somnolence, disorientation, pruritis, or twitching. The initial examination then reveals marked nitrogen retention in the blood. Occasionally the patient goes first to a stomach specialist because of the onset with gastric symptoms. On unusual occasions convulsions or other manifestations of hypertensive encephalopathy are the first indication of the disease. Rarely the first symptom is impairment of vision from hypertensive retinal lesions, which leads the patient to consult an ophthalmologist. Nowadays it is common for glomerulonephritis to be revealed first by proteinuria or hypertension discovered in an insurance or periodic physical examination.

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The "Malignant Phase" of Chronic Glomerulonephritis.—In some cases of chronic glomerulonephritis a sequence of events occurs which

intervention of these other factors that there is no strict parallelism between the lowering of the blood proteins and the extent of the edema—a fact which has led some investigators mistakenly I believe to depreciate the significance of the lowered protein content of the blood in the production of the edema of chronic glomerulonephritis

When edema appears in patients with old secondary contracted kidneys it is usually the result of cardiac weakness and perhaps hypoproteinemia

Hypertension.—Arterial hypertension is a cardinal symptom of chronic glomerulonephritis There are nevertheless cases in which elevation of blood pressure is completely absent or but slight over long periods of time This is particularly true in the nephrotic type of the disease with extensive nephrotic edema in which there may be normal blood pressure over a period of years so that the differentiation from chronic nephrosis is very difficult However if the blood pressure is measured daily in such patients transitory rises to 130 or 140 mm systolic and 90 or 95 mm diastolic pressure in a young adult confined to bed may reveal the tendency to hypertension Particularly in children hypertension is relatively often not demonstrable with certainty Ultimately even those cases which had normal blood pressure during the nephrotic stage develop hypertension When chronic glomerulonephritis affects tuberculous or other cachectic patients hypertension is often completely absent

The hypertension may attain an extreme degree such pressures as 250 mm systolic and 150 mm diastolic are not rare Most often however the blood pressure does not attain such exorbitant heights Particularly in the first years of the disease it is most common to find the pressure well under 200 mm systolic and 120 mm diastolic As the disease lasts longer the tendency is for the blood pressure to become higher though this is by no means invariable Not uncommonly especially in the early stages the rise in the diastolic pressure is proportionately greater than that in the systolic so that such tensions as 170 mm systolic and 130 mm diastolic are encountered But there are also cases in which the systolic rise is the more prominent

In general the blood pressure is not as labile as in the earlier stages of essential hypertension But if the blood pressure is measured several times a day it will almost always be found that there is considerable variation the tendency is for the late afternoon pressure to be higher Leaving bed may also cause a rise in pressure With cardiac failure there may be a fall in blood pressure although except terminally this is not seen as often as in essential hypertension In other cases myocardial insufficiency is not accompanied by decreased blood pressure (Chapter 26)

In the recurrent cases the blood pressure may rise with each exacerbation to fall to normal between the acute attacks When the disease is of the nephrotic type the hypertension present during the acute stage may disappear completely to reappear after months or years usually as the edema is lessening There is thus a complete change of the clinical picture from one dominated by edema and simulating chronic nephrosis to a complex in which cardiovascular phenomena are the central features and simulating essential hypertension

is but minimal, unless it is due to cardiac failure In the recurrent cases edema may appear with each exacerbation over a period of years In the nephrotic type of glomerulonephritis, the anasarca and effusions into serous cavities may be as extreme as in chronic nephrosis If edema is present at all in secondary contracted kidney it is usually due to cardiac insufficiency

Three pathogenetically distinct varieties of edema—nephritic, nephrotic and cardiac—are encountered in chronic glomerulonephritis

Nephritic edema is a manifestation of active glomerulonephritis It is, therefore, met with in the early stages and also during acute exacerbations Sometimes such reactivation is evidenced, in addition to the edema, by the appearance or increase of hematuria As was pointed out in Chapter 6, nephritic edema is not correlated with diminution in the protein content of the blood While nephritic edema may be very extensive (particularly if fluid and salt are not restricted) much more often this is not the case and the edema may be confined solely to a puffiness of the eye-lids most marked in the morning Such bouts of slight edema are indicative of exacerbation of the glomerulonephritis

Nephrotic edema occurs in glomerulonephritis when the patient has lost so much albumin in the urine that the albumin content of the blood is greatly diminished Such edema is characterized by fluid extremely poor in protein and often opalescent it occurs only in the presence of the typical "chemical blood picture" of loss of large amounts of albumin in the urine *i e* usually diminished total protein content inversion of the albumin to globulin ratio and generally increase in blood lipids Usually it takes several weeks or months of copious albuminuria to produce nephrotic edema Once the edema appears, however it is apt to be very extensive and protracted lasting for months or even with remissions for over a year If impairment of renal function appears the proteinuria usually diminishes the blood proteins consequently rise and the edema clears up though the patient is really worse

In cases of the nephrotic type of glomerulonephritis followed from the initial acute attack the following sequence of events may be observed Edema appears at the very onset This nephritic edema is usually slight and of brief duration it occurs in the absence of either hypoproteinemia or heart failure Subsequently—and this may be after weeks months or years—the albuminuria depletes the plasma albumin and nephrotic edema appears The edema at this stage is often massive that it is nephrotic is revealed by the hypoproteinemia and the absence of nephritic activity as shown by the paucity of red cells in the urine

Of course such a schematic course of events is not the rule in chronic glomerulonephritis though I have seen many cases in which the precise sequence just described could be followed More often the factor of capillary damage due to nephritic activity is still present after the plasma proteins have been depleted by the copious and protracted albuminuria The "activity" of the nephritic process in the capillaries is demonstrated by the presence of red blood cells in great or moderate number in the urine There is thus a combination of nephritic and nephrotic edema in the same patient and, as a result of the hypertension and perhaps myocardial damage, cardiac weakness may ensue and also tend to cause edema It is because of the

intervention of these other factors that there is no strict parallelism between the lowering of the blood proteins and the extent of the edema—a fact which has led some investigators mistakenly I believe to depreciate the significance of the lowered protein content of the blood in the production of the edema of chronic glomerulonephritis

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The hypertension results in left ventricular hypertrophy For a long period, often many years, the hypertrophied left ventricle may successfully cope with the increased work and there is no evidence of dilatation During this period, the apex beat is within normal limits, and percussion as well as the roentgen picture reveal no lateral displacement of the cardiac borders However the signs described in Chapter 26 may demonstrate the existence of hypertrophy of the left ventricle At times it is remarkable how long the hypertrophied left ventricle continues to meet great arterial hypertension without dilating There are patients with chronic glomerulonephritis who have a blood pressure as high as 230/140 mm for several years with little or no enlargement of the cardiac shadow in the teleoroentgenogram Finally if the patient is not previously carried off by uremia or some complication as most frequently happens the left ventricle gives way and dilates the left border moving outward Following this the right heart also hypertrophies and dilates as is described in detail in Chapter 26

Clinically for years there is no outspoken evidence of cardiac insufficiency in most cases of chronic glomerulonephritis the chief danger always being renal insufficiency But it is probable that in some instances the final diminution in urinary volume which sends the patient with impaired renal function into uremia is due to relative myocardial insufficiency It is true that in many cases the blood pressure does not drop with the advent of cardiac insufficiency but in such cases the blood pressure may be maintained in the face of decreased cardiac output only by augmented arteriolar constriction which includes the kidney and diminishes renal blood flow And the progressive destruction of more renal parenchyma demands an even higher blood pressure than previously to maintain the compensatory polyuria (see below)

There are long standing cases of chronic glomerulonephritis (secondary contracted kidney) in which the clinical picture of cardiac insufficiency develops There may be such evidences of left ventricular failure as attacks of pulmonary edema cardiac asthma gallop rhythm and drop in blood pressure Or if the right heart has also given way engorgement of the liver edema of the feet cyanosis and other evidences of congestive heart failure may appear It is to be emphasized that such a purely cardiac picture is decidedly unusual in chronic glomerulonephritis the typical ending is uremia But in the late stages of uremia heart failure often adds to the misery

The hypertension may cause other manifestations than those due to its effect on the heart The headaches so often present in patients with good renal function and no evidence of cerebral arteriosclerosis are doubtless often the result of the hypertension Such headaches may accompany paroxysmal rises in blood pressure and are probably manifestations of hypertensive encephalopathy Epistaxis is a common occurrence and may be very profuse Cerebral hemorrhage is unusual in chronic glomerulonephritis but does occur especially in older individuals Doubtless cerebral hemorrhage is far rarer in chronic glomerulonephritis than in essential hypertension because patients with the former disease are usually much younger and their cerebral vessels are not so often markedly atherosclerotic Occasionally such angiospastic phenomena as dead fingers

are encountered A common phenomenon correlated with the hypertension is spasticity of the radial and other large arteries Moschcowitz[a] has found that it may appear with paroxysms of hypertension and vanish when the pressure goes down

Hypertensive Encephalopathy —Hypertensive encephalopathy may occur but is not as common as in acute glomerulonephritis It usually appears in the earlier periods of the disease and may recur at intervals over a period of years as in the case reported by Oppenheimer[22] and the author The probability that some of the headaches that are so frequent in this disease are manifestations of hypertensive encephalopathy was mentioned above

Retinal Lesions —Retinal changes are common in chronic glomerulonephritis being present in a majority of cases for a varying period preceding the fatal outcome In 55 cases of chronic glomerulonephritis studied by the author and Oppenheimer[23] the fundus was negative in 24 retinal arteriosclerosis with or without consequent retinal lesions was present in 14 and hypertensive neuroretinopathy was present in 17 By carefully following up their patients Cannady and O Hare[24] were able to demonstrate severe retinal lesions in 25 of 32 individuals Retinal lesions occur only in the cases with arterial hypertension and are the more frequent the higher the blood pressure they may be found in the absence of any impairment of renal function Nevertheless most although not all patients with retinal changes ultimately develop renal insufficiency if it is not present before the retinal lesions appear The very bad prognostic significance of hypertensive neuro-retinopathy has already been discussed (page 380) Retinal arteriosclerosis and arteriosclerotic retinopathy develop in chronic glomerulonephritis only after hypertension has been present for a number of years and are not ophthalmoscopically discernible in by any means all such cases It was mentioned above that chronic glomerulonephritis may first be discovered by the ophthalmologist through finding hypertensive retinal changes Worthy of emphasis is that contrary to the malignant phase of essential hypertension it is not rare for chronic glomerulonephritis to run its entire course and terminate in uremia with no changes in the retina or optic disc

A slight degree of *exophthalmus* is not rare in severe cases of chronic glomerulonephritis Barker and Hanes[25] observed exophthalmus in 16 of 33 patients with chronic nephritis a much higher incidence than I have noted They found exophthalmus most often in uremic or suburemic patients Dr A A Epstein who called my attention to the phenomenon has also observed it especially in cases which are progressing rapidly Exophthalmus has seemed to me more common in the malignant phase of essential hypertension than in chronic glomerulonephritis It is often associated with increased intracranial pressure due to edema of the brain

Impairment of Renal Function and Uremia —These are the dangers which always confront the patient with chronic glomerulonephritis and which sooner or later terminate the life of most such sufferers However in some of the cases renal function is not demonstrably impaired for long periods even many years The patient is able to elaborate a urine of high specific gravity excrete dyes or other substances satisfactorily and the blood chemistry is normal The only sign of the disease at this period may be

The hypertension results in left ventricular hypertrophy For a long period often many years the hypertrophied left ventricle may successfully cope with the increased work, and there is no evidence of dilatation During this period, the apex beat is within normal limits, and percussion as well as the roentgen picture reveal no lateral displacement of the cardiac borders However, the signs described in Chapter 26 may demonstrate the existence of hypertrophy of the left ventricle At times it is remarkable how long the hypertrophied left ventricle continues to meet great arterial hypertension without dilating There are patients with chronic glomerulonephritis who have a blood pressure as high as 250/140 mm for several years with little or no enlargement of the cardiac shadow in the teleroentgenogram Finally if the patient is not previously carried off by uremia or some complication as most frequently happens the left ventricle gives way and dilates the left border moving outward Following this the right heart also hypertrophies and dilates as is described in detail in Chapter 26

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4 In some patients with old glomerulonephritis the blood pressure rises to very high levels and the classical picture of malignant hypertension develops—violent headache, hypertensive retinopathy and acute depression of renal function with uremia that often progresses rapidly. *Arteriolar* necrosis is found. In these cases the renal failure is due to acute renal arteriolar damage resulting from great diastolic hypertension; the course of events is similar to what occurs in the malignant phase of essential hypertension.

5 Occasionally drastic salt restriction or the immoderate use of mercurial diuretics seems to precipitate azotemia and uremia. In such cases the plasma sodium level is low and the nonprotein nitrogen of the blood may fall when salt is given.

As a rule once renal function has been impaired in chronic glomerulonephritis it does not improve. Often deterioration is exceedingly slow, no change being apparent for years, but such alteration in renal function as does occur is usually for the worse. However, there are exceptional instances in which, for no apparent reason, renal function as measured by the concentrating power does improve, a fact which I have several times observed. In cases with exacerbations renal function may suffer during the acute episodes, to improve with the passing of the acute exacerbation.

The impairment of renal function sooner or later leads to clinically obvious uremia. However, it is common for azotemia to be present for a year or more without subjective symptoms of uremia. And there are rare cases of glomerulonephritis in which moderate azotemia (blood urea nitrogen 30 to 50 mg per cent) lasts even three or four years while the patient is still able to work. The symptomatology of uremia in chronic glomerulonephritis does not differ from that of uremia produced by other diseases and has been discussed in Chapter 7.

Tubular Failure in Chronic Glomerulonephritis.—In chronic glomerulonephritis the functional disturbance is primarily impairment of glomerular filtration. However, tubular function is also defective. This may be revealed in patients with long standing polyuria and hyposthenuria by the excretion of so much water and electrolyte in the urine that dehydration develops. They may continue to excrete sodium and chloride in the urine despite plasma levels at which normal kidneys would conserve these ions. The dehydration may be immediately obvious from the dry inelastic skin and dry tongue. Dehydration is especially apt to occur if the hyposthenuric patient is on a salt poor diet or is losing electrolyte and water by vomiting. The fundamental cause of the salt and water depletion is probably that so small a number of nephrons have survived that the volume of filtrate passing down each tubule is too great for adequate processing by the diseased tubular cells. The consequence is that too high a proportion of water and electrolytes escapes reabsorption. As a result of such inadequate conservation of water and electrolytes in chronic glomerulonephritis dehydration often becomes a prominent and not rarely a dominant feature of the clinical picture. The depletion of water and electrolytes reaches its apogee in the cases that have been termed salt losing nephritis; they are described below.

proteinuria But the danger of renal failure is always present and sooner or later it appears usually insidiously, in the great majority of cases

The tempo with which impairment of renal function progresses in chronic glomerulonephritis varies immensely from case to case In some instances renal insufficiency is severe from the start and progresses to fatal uremia within months In such subacute cases necropsy generally shows in addition to severe changes in the walls of and within the loops extracapillary glomerulonephritis with extensive formation of epithelial crescents, there may also be necrosis of afferent arterioles and glomerular loops In other cases renal function first becomes significantly impaired only after years or even decades of proteinuria During this period the patient may succumb to an intercurrent ailment without ever having had azotemia or even hyposthenuria

Once renal function has been sensibly damaged the impairment may progress slowly or rapidly Some patients remain in the compensated stage of impaired renal function for years while others quickly decompensate

A patient in the compensated stage of impaired renal function has a daily urinary volume of 2 or 3 liters or rarely more The specific gravity is low even during water privation the patient cannot elaborate a concentrated urine In the most severe impairment the highest specific gravity that can be attained is 1 010 at which concentration the urine is approximately isotonic with the blood As a result of the polyuria the patient suffers from nocturia and is thirsty drinking large quantities of water Despite the copious ingestion of water the skin may be dry and inelastic and the patient appear generally dehydrated presenting an appearance akin to that so often seen in patients with long standing prostatic obstruction During the compensated stage azotemia is absent

Sooner or later most patients with compensated impairment of renal function decompensate *i e* azotemia and uremic symptoms develop This occurs under several circumstances

1 In most long-standing cases of glomerulonephritis the aggravation of the impairment of renal function sets in insidiously and without evident cause With no obvious incitant weakness anorexia nausea vomiting or other uremic symptoms or anemia appear and azotemia is discovered Or a periodic examination of a known nephritic reveals azotemia while he still feels well In these cases the progression of the uremia is often slow and low grade azotemia may last for years The retina is often negative in these patients Anatomical examination generally reveals far advanced hyalinization and extensive obliteration of the glomeruli with atrophy of the appertaining tubules The arterioles may show hyalinization and the small arteries cellular and fibrous intimal thickening Acute changes in the glomeruli are not prominent and arteriolar necrosis is absent

2 In other cases usually of relatively short duration the renal failure is due to an acute exacerbation of glomerulonephritis with hematuria following a sore throat or other infection Here the kidneys reveal acute lesions in addition to the long standing changes

3 Heart failure sometimes precipitates renal insufficiency in a patient with long standing hyposthenuria

go on to coma The dry and inelastic skin evinces the dehydration Anemia develops The blood pressure is normal or low but there is no pigmentation other than perhaps that due to urochrome page 212) which is yellowish and does not involve the mucous membranes Proteinuria is usually not massive and may be absent for considerable periods There is hyposthenuria usually polyuria azotemia hyponatremia hypochloremia and usually acidosis Observations by Earle and Murphy and their associates showed that renal blood flow glomerular filtration and maximum tubular excretion (PAH) and reabsorption (glucose) are all depressed Large amounts of sodium are lost in the urine with the result that high salt intake is necessary to maintain the patient More remains to be learned about the potassium exchange In Earle s case the loss of potassium was excessive with resultant hypokalemia In Murphy s patient serum potassium reached as high as 7 4 mEq per liter except when hypokalemia resulted from massive infusions of sodium salts and dextrose In Nussbaum s patient the electrocardiogram was indicative of hyperpotassemia The differential diagnosis from Addison s disease is facilitated by the therapeutic response to sodium salts but not to adrenal cortical hormones normal depression of the eosinophile count by ACTH normal ketosteroid content of the urine and normal glucose tolerance curve

The syndrome of salt losing nephritis has been observed to result from glomerulonephritis pyelonephritis and perhaps congenital cystic disease It appears that the syndrome is more apt to result from pyelonephritis than from glomerulonephritis presumably because in the latter parenchymal disease starts with and is more pronounced in the tubules In at least three of the reported cases there were extensive cystic dilatations of the tubules

The patient can be maintained only by large supplements of sodium chloride If there is acidosis sodium bicarbonate may also be required When the patient is vomiting the sodium salts have to be given intravenously The required supplements of sodium salts may exceed 20 grams a day Repeated transfusions are needed in some cases By such measures Nussbaum s patient was maintained for a year after the blood urea nitrogen was 168 mg per cent

The Blood —The non protein nitrogen shows no abnormalities as long as renal function is unimpaired or such impairment is compensated With the advent of renal decompensation the characteristic changes in the diffusible constituents occur (page 57)

The proteins and lipids of the plasma are likewise unchanged unless there is copious loss of protein in the urine Proteinuria of sufficient degree to deplete the plasma proteins is generally found in the early stages but may continue for many months or even years in the so-called nephrotic type of glomerulonephritis In such cases the typical nephrotic changes—diminished total protein inversion of the albumin to globulin ratio increase in fibrinogen increase in fat and lipoids—are found These changes in the colloids differ in no wise from those encountered in chronic nephrosis and may be quite as severe as in the latter disease For further details the reader is referred to Chapter 16 When impairment of renal function supervenes in the nephrotic type of glomerulonephritis the proteinuria

Individual Renal Functions.—Detailed analysis of individual renal functions by the methods of Homer Smith's school was carried out by Earle[35] *et al.* Similar data have been obtained by Corcoran[36] and his associates, Hilden,[37] Cargill and Hickam,[38] Hogeman,[39] and others. They reveal that renal blood flow, glomerular filtration and tubular function as measured by clearance techniques are all reduced. Until the terminal stage, filtration is reduced more than blood flow (low ratio of inulin to PAH clearance) with the result that the filtration fraction is low. In the late stages the filtration fraction is higher. The predominance of glomerular over tubular damage in the early stages is revealed by the observation of Earle *et al.* that the ratio of the filtration rate to the functional tubular mass (diodrast Tm) is low; later, with progressive tubular damage this proportion becomes higher. Similarly, Hilden found evidence of predominant glomerular damage in early cases and those in the nephrotic phase in the form of a low ratio of the urea to the diodrast clearance. Contrariwise, in the terminal stage and in the hypertensive form of the disease Hilden observed that the urea clearance is high in comparison to that of diodrast. Chasis and Smith[40] demonstrated that in chronic glomerulonephritis with hyposthenuria the proportion of urea which undergoes back-diffusion decreases, with the result that the urea/inulin clearance ratio approaches unity.

By catheterization of the renal vein Cargill and Hickam found that in chronic glomerulonephritis with decreased renal blood flow the oxygen consumption of the kidney is decreased but the extraction percentage is normal.

The question of the functioning of aglomerular tubules in chronic glomerulonephritis has already been discussed (page 609). Inadequate tubular conservation of water and electrolytes in chronic glomerulonephritis with resultant dehydration often becomes a prominent and rarely a dominant feature of the clinical picture. The depletion of water and electrolyte reach their apogee in the rare cases described in the next paragraphs.

Salt-Losing Nephritis.—There are very rare cases of renal disease in which salt and water depletion is so severe that the patient goes into a shock-like state. Such cases were first described by Thorn[41] and his associates under the name of "salt losing nephritis." They reported two patients with chronic renal disease (one had chronic glomerulonephritis and the other probably chronic pyelonephritis with extensive cystic change) and normal adrenals in whom the signs and symptoms were indistinguishable from those of acute adrenocortical insufficiency. However, while adrenocortical hormones were of no help, sodium chloride and bicarbonate produced prompt improvement. Since then, cases of such salt losing nephritis have been described by Sawyer and Solez[4] (glomerulonephritis and tubular calcification), Borst[43] (cystic disease, probably congenital), Nussbaum[44] *et al.* (chronic pyelonephritis), Earle[45] *et al.* (patient still living) and Murphy[46] *et al.* (chronic pyelonephritis). I had the privilege of seeing the patient studied by Nussbaum and two others in whom the syndrome was probably also due to chronic pyelonephritis. The cases are usually of insidious onset with a history of such symptoms as weakness, anorexia, emaciation, nausea and vomiting. Mental confusion and drowsiness may

go on to coma The dry and inelastic skin evinces the dehydration Anemia develops The blood pressure is normal or low but there is no pigmentation other than perhaps that due to urochrome page 212) which is yellowish and does not involve the mucous membranes Proteinuria is usually not massive and may be absent for considerable periods There is hyposthenuria usually polyuria azotemia hyponatremia hypochloremia and usually acidosis Observations by Earle and Murphy and their associates showed that renal blood flow glomerular filtration and maximum tubular excretion (PAH) and reabsorption (glucose) are all depressed Large amounts of sodium are lost in the urine with the result that high salt intake is necessary to maintain the patient More remains to be learned about the potassium exchange In Earle's case the loss of potassium was excessive with resultant hypokalemia In Murphy's patient serum potassium reached as high as 7 4 mEq per liter except when hypokalemia resulted from massive infusions of sodium salts and dextrose In Nussbaum's patient the electrocardiogram was indicative of hyperpotassemia The differential diagnosis from Addison's disease is facilitated by the therapeutic response to sodium salts but not to adrenal cortical hormones normal depression of the eosinophile count by ACTH normal ketosteroid content of the urine and normal glucose tolerance curve

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diminishes, following this, the blood proteins increase the albumin to globulin ratio tends to normal, and the lipemia diminishes Accompanying these changes the edema diminishes and there occurs the shift in the clinical picture which was mentioned above from one resembling chronic nephrosis to one simulating essential hypertension

ANEMIA —Quincke[48] and Hunter[49] long ago pointed out that renal disease may produce anemia Some patients with chronic glomerulonephritis come to the physician because of pallor or other symptoms of anemia Anemic symptoms may dominate the clinical picture for a year or more and repeated transfusions may be required to maintain the patient It has seemed to me that such cases of protracted azotemic anemia have become more common in recent years, perhaps because the life of azotemic patients has been prolonged by better dietary management and more transfusions The anemia may be very severe Red cell counts below 2,000 000 and hemoglobin content below 6 grams are not rare The severity of the anemia is correlated with the impairment of renal function there is a rough inverse parallelism between the hemoglobin and nonprotein nitrogen of the blood (Ashe[50] Townsend[51] *et al*) In the exceptional cases with anemia in the absence of azotemia the origin of the former is probably other than renal In some such cases anorexia or dietary restrictions may be concerned and they may of course abet the azotemic cases Protein depletion due to proteinuria apparently is not concerned in the genesis of the anemia in the nephrotic phase without azotemia anemia is characteristically absent

The anemia is most often normocytic Of 44 patients with azotemic anemia studied by Callen and Limarzi[5] 34 had normocytic normochromic 2 microcytic hypochromic and 8 macrocytic anemia

The pathogenesis of the anemia is obscure Characteristic of at least the large majority of the cases is that they are not influenced by the administration of iron liver folic acid or vitamin B_{12} The reticulocyte count is not increased Nor is the bilirubin content of the serum above normal Studies of the bone-marrow by Townsend and his associates revealed the latter to be normal or hyperplastic the hyperplasia was of normoblastic and never of megaloblastic type Similarly Callen and Limarzi s studies of the bone marrow in nephrogenic anemia disclosed hypercellular marrow in 80 per cent of the cases The hypercellularity involved mainly the myeloid cells and megakaryocytes with normal erythropoiesis They found hypoplasia of the erythroid tissue only when the nonprotein nitrogen of the blood exceeded 150 mg per cent Townsend *et al* found that while 22 of 27 nephritics without anemia had normal gastric acidity all of 19 with anemia had diminished acidity after an alcohol meal 11 of these had anacidity after the alcohol meal and 5 still had anacidity after histamine They believe that the gastric secretory disturbance plays an important part in producing the anemia through causing a deficiency of building material for red cell formation However this interpretation does not accord with the occasional finding of ample free acid in patients with azotemic anemia Callen and Limarzi point out that the development of azotemic anemia in the presence of histologically normal erythroid tissue in the bone marrow indicates defect in the delivery rather than the development of the red

cells This defect results from renal insufficiency and is correlated with azotemia but the actual nature of the connection is unknown On the basis of the survival time of transfused red cells and a variety of other evidence Loge *et al* [35] conclude that in anemia due to chronic renal insufficiency there is always depression of erythropoiesis to which is added in some cases an extracorpuscular hemolytic factor

It has been thought particularly by French authors (Labbé and Salomon [33] Lortat-Jacob and Gassier[34]) that the picture of true pernicious anemia may be produced by chronic nephritis I have not observed this and agree with Naegeli [35] that such cases are probably instances of true pernicious anemia in which the renal manifestations are well marked (see page 459) or else accidental complications Study of the bone marrow and absence of response to vitamin B_{12} readily differentiate azotemic from pernicious anemia

The blood *platelet* count is usually within normal limits even when anemia is severe or when a hemorrhagic diathesis develops The latter is a uremic manifestation and apparently due to capillary damage not only the platelet count but also the prothrombin concentration are unchanged

The *white cells* show no constant change in patients with azotemic anemia Sometimes there is slight leucocytosis with a modest shift to the left in the absence of obvious infection

The Urine —*Proteinuria* is an almost constant manifestation of chronic glomerulonephritis In cases of very long standing (secondary contracted kidney) the proteinuria is often but slight and rarely even absent during some examinations In the earlier stages of chronic glomerulonephritis the proteinuria is usually very copious This is particularly so in the nephrotic type of the disease in which a very high degree of proteinuria may be present continuously for months and years In such cases the urinary protein is mostly albumin When impairment of renal function appears the proteinuria diminishes the quantity of protein in the urine being a poor prognostic indicator under such circumstances

Casts accompany the protein in the urine All varieties—hyaline granular epithelial fatty etc —may be found during the active stages of the disease With diminution of proteinuria in the later phases casts also diminish in number and become very sparing It is common when the stage of secondary contracted kidney with hyposthenuria has been reached to find only rare casts Accompanying the casts in the nephrotic type of the disease are doubly refractile lipoids which may be as abundant as in chronic nephrosis

Hematuria is another frequent finding In the earlier periods of the disease and during acute exacerbations there may be sufficient blood in the urine to be detected with the naked eye More often however there is only microscopic hematuria Later in the course of the disease the number of red cells present in the urine diminishes and they are most often scanty in cases of secondary contracted kidney The same is often true in the nephrotic type of the disease so that absence of red blood cells from the urine does not establish the diagnosis of chronic nephrosis in a patient presenting a nephrotic picture The presence of large numbers of red cells in the urine is usually indicative of an active inflammatory

process in the glomeruli If the disease enters the malignant phase (page 614), augmented and even gross hematuria may result from necrosis of renal arterioles and glomerular loops

The volume and specific gravity of the urine have already been discussed

Gastro intestinal Symptoms —Gastro-intestinal symptoms, such as nausea vomiting and diarrhea are most often uremic manifestations They may, perhaps, also be due, in patients with general edema to edema of the mucous membrane of the alimentary tract However, this often offered explanation has not been proved In the malignant phase with extreme hypertension, nausea and vomiting may result from edema of the brain In other cases however these symptoms occur in the absence of nitrogen retention, extreme hypertension or edema, their origin being obscure

Headache —Headache is a very common and often initial complaint It may be of uremic nature or else result from the hypertension

Pains in the Kidney Region —Pains in the kidney region are decidedly uncommon in chronic glomerulonephritis However, there are rare instances in which they are severe and protracted (so-called nephritis dolorosa) They usually consist in a dull ache in the lumbar region, but are rarely sharp and radiate to the genitalia and thighs They have been attributed to swelling of the kidney with stretching of the capsule and to thickening and adhesions of the capsule Lichtwitz[6] observed such pains in a patient who had a decapsulation during the acute stage which presumably produced subsequent capsular adhesions

General Condition —During long periods despite the presence of hypertension and proteinuria the patient may feel relatively well Such a patient may have no impairment of his working capacity for many years and may even appear ruddy though more often he is pale But during the active and progressive phases of chronic glomerulonephritis weakness and anorexia are usually well marked and ultimately with the advent of uremia, become extreme During these periods there is usually a waxy pallor which in combination with more or less puffiness of the eye lids constitutes the nephritic facies that often enables one to suspect renal disease at the first glance With the advent of isosthenuria the skin is is usually very dry even in mid-summer and perspiration is difficult to induce the hair tends to fall out When renal insufficiency lasts for a long time particularly when it is accompanied by protracted vomiting and diarrhea, the emaciation may be frightful rivalling that seen in cancerous cachexia

Renal Dwarfism and Renal Osteodystrophy —Children who have suffered for a long time from renal insufficiency are often retarded in their development This developmental retardation may be associated with bone deformities and was called renal dwarfism by Barber,[57] other authors use the terms renal infantilism and renal rickets Cases were soon after described in this country by Shipley[58] and his coworkers Lathrop[59] Schoenthal and Burpee[60] and others Albright[61] and Jaffe[6] and their associates have contributed importantly to understanding of the mechanism of osseous involvement in renal disease

Some of the cases of gross skeletal disease of renal origin in children are due to glomerulonephritis or pyelonephritis setting in early in life. In a high proportion, however, there is a primary congenital anomaly of the urinary passages with secondary hydronephrotic or pyelonephritic contraction of the kidneys. Ellis and Evans[63] made the interesting observation that in 14 of 17 cases of renal dwarfism the contracted kidney was accompanied by dilatation and hypertrophy of the bladder and usually by hydronephrosis and dilatation of the ureters. Since no obstruction was found they suggest that the dilatation is due to defective control of the urethro-vesical sphincter. However, since the deficient concentrating ability of these patients leads to marked polyuria over a period of years, it is also possible that the dilatation of the urinary tract is an adaptation of the youthful organism to the increased urinary volume. Congenital polycystic disease may be responsible. There are rare and remarkable cases in which the skeletal deformities are part of a complex clinical picture (known as the Fanconi syndrome) which seems to result from a congenital metabolic anomaly of the renal tubules, one of the manifestations of which is deficient tubular reabsorption of calcium (cf. page 32).

The child is usually considerably below the average height, and in adolescent children the secondary sexual characteristics are retarded. The gross skeletal deformities and, as a result of the changes in the epiphyses, the roentgen appearance often resemble those of rickets, although the histological changes are fundamentally different (see below). Knock-knee seems to be the most common deformity and may be very severe. There are often thickening of the epiphyses of the long bones, beading of the ribs, thoracic deformities, bossing, etc. I have seen a case following long-standing hydronephrotic atrophy of the kidneys in which the bony changes were accompanied by marked atrophy of the muscles of the thigh. Such cases have been admitted to orthopedic hospitals because of the deformity without knowledge of the renal lesions and have even been operated upon. The roentgen appearance of the bones, which varies greatly in different cases but often resembles the changes of rickets, is described in detail by Parsons.[64] In some instances rarefaction of the skeleton is very widespread. Metastatic calcification may occur in the vicinity of the joints, in the media of arteries and elsewhere.

In chronic renal insufficiency in adults it appears from the detailed studies of Ginzler and Jaffe[65] that "there almost regularly occur skeletal changes consisting in more or less pronounced fibroporotic resorption of bone accompanied by a varying amount of new bone formation. In the vast majority of cases, however, these changes are slight and demonstrable only by histological study." Only very rarely and after many years does renal insufficiency in adults produce osseous changes similar to those just described in children. Albright, Drake and Sulkowitch[66] have published in detail one such case and cite two others; in their patient the osseous lesions were accompanied by calcium deposits in the neighborhood of joints and medial calcification of the arteries. The osseous changes in adults who have suffered from long-standing renal insufficiency have been studied in detail by Dr. Henry L. Jaffe, who has very kindly given me the following brief summary of his observations: "In adults who have suffered

from chronic renal insufficiency, the *bones though* usually not altered grossly, often reveal on microscopic examination mild but clear-cut fibroporotic changes in the spongiosa *In these* cases the spongy trabeculæ show scattered resorption lacunæ containing osteoclasts and connective tissue, and some of them may also present, here and there deposits of new bone Occasionally—and specifically when the renal insufficiency has been very protracted—*the bones will be found* even grossly altered In these cases the spongiosa is close-meshed and *the trabeculæ* are thickened and distorted, so that altogether the condition amounts to an osteosclerosis The microscopic findings indicate that the osteosclerosis has developed through the gradual accretion of new *bone, despite* the alternation of reparative with resorptive processes that must have been going on for a long time *According to Albright* and Reifenstein the histological changes in renal osteodystrophy are histologically indistinguishable from those in generalized osteitis fibrosa due to primary hyperparathyroidism but in children they are associated with changes in the epiphyses which do not occur *in hyperparathyroidism* and in the *x*-ray picture resemble those of true rickets

While the pathogenesis of the osseous changes due to renal insufficiency has not been altogether elucidated the process is doubtless an osteodystrophy resulting from the disturbances in mineral metabolism produced by *the impairment in* renal function That impairment of renal function *favors the development* of the osseous changes in question is shown by the experiments of Pappenheimer[66] He found that reduction of renal tissue in *young rats* which are kept on a calcium poor diet results in skeletal lesions closely resembling renal osteodystrophy and far exceeding those attributable *to the calcium* deficiency alone Lyttle[67] pointed out that the gross skeletal deformities occur almost exclusively in those instances of renal disease that set in very early in life when growth is most rapid and before *union of the* epiphyses The bony lesions apparently occur only in children with long standing impairment of renal function as demonstrated by inability to elaborate urine of normally high concentration Sooner or later the impairment of renal function becomes decompensated nitrogen retention appears, and the child ultimately succumbs to uremia Histological studies (*cf* Albright[65] *et al* and Shelling and Remsen[68]) indicate that the changes in the bones are fundamentally the same as those present in primary parathyroid adenoma and those which were produced by Jaffe[69] and his coworkers by the continuous administration of parathyroid extract—conditions in which hyperparathyroidism leads to excessive mobilization of calcium from the skeleton The problem of the pathogenesis of renal osteodystrophy is thus really that of the mechanism by which renal insufficiency leads to the removal of excessive quantities of calcium from the skeleton Several factors may be involved

1 The ability of the insufficient kidney to form a highly acid urine and to synthesize ammonia is decreased page 45) In consequence of inadequate urinary acidity and ammonia formation the organism is compelled to excrete fixed base in order that the acid end products of metabolism may be eliminated Among the fixed base on which the organism

draws is that stored in the bones and there thus results decalcification of the skeleton

2 Overlapping the preceding factor is the severe and protracted acidosis from which patients with renal insufficiency suffer Jaffe[70] and his associates produced osteitis fibrosa the type of bone lesion here in question by inducing chronic acidosis The acidosis entails a drain on the fixed base of the body including the calcium of the skeleton

3 The impairment of glomerular filtration entails phosphate retention which tends to depress the calcium content of the blood and favors mobilization of the mineral from the bones Mitchell and Guest[1] suggest that as a result of the deficient renal excretion of phosphate more of this ion is eliminated into the intestine and there interferes with the absorption of calcium through the formation of insoluble calcium phosphates thereby favoring calcium deficiency and consequent skeletal changes

Both glomerular insufficiency (retention of phosphate and other anions) and tubular failure (inadequate reabsorption of calcium and other kations) may thus participate in the genesis of the skeletal changes their relative importance varies in different types of renal disease (cf Albright and Reifenstein[72])

Evidence has been accumulated which indicates that whatever the precise mechanism through which renal insufficiency produces the osseous changes it is associated with hyperplasia and hyperfunction of the parathyroid glands Pappenheimer[66] showed that reduction in renal tissue in young rats leads to enlargement of the parathyroids Pappenheimer and Wilens[7] found that the weight at necropsy of the parathyroids from nephritics averages more than 50 per cent greater than those of controls Highman and Hamilton[74] demonstrated that there is increased activity of the parathyroid glands in chronic renal disease as measured by the effect of the blood on the calcium content of the blood in rabbits In the above mentioned case of Albright the parathyroids weighed no less than 11 grams Albright and his associates have advanced the hypothesis that the stimulus to the hyperplasia of the parathyroids is phosphate retention they were able to produce parathyroid hyperplasia by the injection of phosphate Nevertheless Albright and Reifenstein are not of the opinion that the osseous lesions are due directly to the secondary hyperparathyroidism for they found that the bone disease responds better to measures which overcome acidosis than to elimination of phosphate retention

The unusual instances in which improvement of the osseous changes has seemed to follow the administration of vitamin D (Gyorgy[75] Karelitz and Kolomoyzeff[76] Peters[77]) do not demonstrate the identity of renal osteodystrophy with ordinary rickets As the latter investigator points out the action of irradiated ergosterol in promoting absorption and storage of calcium and phosphorus is not confined to rickets Much more often antirachitic therapy has little or no effect on the osteodystrophy (Hess[78] and others one personal observation) certainly nothing like the effect that one anticipates in banal rickets As mentioned above the histological changes in renal osteodystrophy are much more closely related to those of hyperparathyroidism than to those of rickets and the term renal rickets is a misnomer

DIAGNOSIS OF CHRONIC GLOMERULONEPHRITIS

As a rule the recognition of chronic glomerulonephritis presents little difficulty In typical cases, the proteinuria, hematuria impairment of renal function, edema, hypertension, etc constitute an unequivocal picture The diagnosis is easier when there is a history of acute glomerulonephritis but this is absent even more often than is a history of rheumatic fever in middle-aged women with mitral stenosis In cases in which the history of acute glomerulonephritis is wanting, and in which only one or two of the just-mentioned manifestations are present the diagnosis may be difficult or impossible for a long time, sometimes until the post mortem examination

In children with proteinuria in the absence of other evidences of renal disease, the question often arises whether the coagulable urine manifests *orthostatic proteinuria* or is due to chronic glomerulonephritis (*cf* page 401)

A frequent dilemma is whether a nephrotic syndrome results from *chronic (lipoid) nephrosis* or glomerulonephritis For the many who do not believe that chronic nephrosis exists as an independent entity the problem does not exist and at present from a strictly pragmatic point of view it is not of much importance In Chapter 16 however evidence is presented that chronic nephrosis is a nosologic entity and its characteristics are described

Differentiation between chronic *pyelonephritis* and glomerulonephritis may be difficult or even impossible In the past most cases of pyelonephritis were mistakenly regarded as glomerulonephritis even at necropsy At present at least in New York City pyelonephritis is the more common of the two disorders The diagnostic difficulties are largely in the cases of pyelonephritis which first come under observation when they have hypertension and/or renal insufficiency Extremely high blood pressure may result from pyelonephritis Either pyelonephritis or glomerulonephritis may produce the clinical picture of malignant hypertension with hypertensive retinopathy The presence of pus clumps in the sediment of course speaks for pyelonephritis apart from rare instances of complication of glomerulonephritis by a urinary tract infection But it must be remembered that in long-standing chronic pyelonephritis when the infection is quiescent or abolished and especially when antibiotics have been given the urine may contain very few white cells And in active glomerulonephritis considerable numbers of polymorphonuclear leucocytes are present in the sediment though there are no clumps A few red cells are not unusual in the centrifuged sediment in pyelonephritis but marked hematuria is rare it may result from hemorrhagic cystitis While during most of the course of chronic pyelonephritis the sediment contains few casts in the terminal uremic stages large granular and waxy casts may be abundant (Lippman [79] own observations) There are cases of chronic pyelonephritis with marked proteinuria but it is never as massive as in the nephrotic stage of glomerulonephritis The urine is sterile in glomerulonephritis while organisms can often be demonstrated in the stained sediment or by culture in chronic pyelonephritis But in many cases of long standing pyelonephritis organisms can not be found Edema occurs only in the late stages of pyelonephritis, is usually slight and is almost always of cardiac

origin Fever and chills may be due to chronic pyelonephritis not rarely the disease is discovered in the search for the cause of obscure pyrexia In chronic glomerulonephritis fever occurs only as the result of a complication. The pyelographic findings may speak for pyelonephritis (page 619) In many cases the history of either acute glomerulonephritis or acute pyelonephritis (especially during pregnancy) clarifies the state of affairs

Another condition that formerly was usually included in the rubric of chronic glomerulonephritis is *intercapillary glomerulosclerosis* in diabetes Actually the recognition of intercapillary glomerulosclerosis rarely presents difficulties When a diabetic without hypertension develops proteinuria retinal lesions or a full fledged nephrotic syndrome there is every reason to believe that the Kimmelstiel Wilson syndrome is evolving When hypertension is present in a diabetic the appearance of proteinuria or retinal lesions brings with it the problem of whether these findings are due to intercapillary glomerulosclerosis or to the very frequent coincidence of diabetes and essential hypertension But glomerulonephritis hardly enters into the differential diagnosis it must be very rare in diabetes I do not recall encountering the coincidence

The differentiation between chronic glomerulonephritis and *focal nephritis* is discussed on page 631 and that between acute glomerulonephritis and an *acute exacerbation* of the chronic disease on page 582

There are cases of chronic glomerulonephritis in which hypertension is associated with only slight proteinuria and but little impairment of renal function When such a case occurs in an individual past youth and there is no history of acute glomerulonephritis or edema the differentiation from *essential hypertension* may be difficult or impossible Actually in some such cases that I have seen the family history and sthenic bodily habitus indicated that the glomerulonephritis had affected an individual with the hereditary basis of essential hypertension The sometimes difficult or impossible differentiation between chronic glomerulonephritis and the malignant phase of essential hypertension is discussed on page 835

In tuberculosis and other long standing suppurations the question formerly arose quite often and still does on rare occasions whether *proteinuria* is due to *amyloidosis* or chronic glomerulonephritis which in such cachectic states usually is not accompanied by hypertension Renal insufficiency or hypertension may occur in either amyloid contracted kidney or glomerulonephritis Evidences of involvement of the liver spleen or intestine may be present in amyloidosis or the latter may be demonstrable by the Congo red test or biopsy (page 525) Any considerable hematuria speaks for glomerulonephritis unless it is due to tuberculosis of the kidney It should be remembered that glomerulonephritis is rare in suppurative tuberculosis while amyloidosis was until recently very common and still is not a rarity Most of the erroneous diagnoses that I have seen have consisted in mistaking amyloidosis for glomerulonephritis and not the reverse

Hematuria and proteinuria in tuberculous patients may give rise to the question whether they are due to *tuberculosis* of the kidneys or chronic glomerulonephritis search for tubercle bacilli and pyelographic and cystoscopic examinations will usually decide

Polycystic kidneys may present a clinical picture akin to that of glomerulonephritis with hypertension, cardiac hypertrophy, hematuria and renal insufficiency; palpation or radiography of the enlarged kidneys will usually reveal them.

Periarteritis nodosa or the *wire-loop lesions of disseminated lupus erythematosus* (page 537) are not rarely difficult to differentiate from chronic glomerulonephritis. Since the urinary changes in periarteritis and disseminated lupus may completely mimic those of glomerulonephritis, recognition of the two former diseases depends on demonstration of their *positive characteristics*. Marked hypertension is very rare in disseminated lupus. In recent years demonstration of the L.-E. cell has been a great help in the recognition of disseminated lupus.

PROGNOSIS OF CHRONIC GLOMERULONEPHRITIS

Prognosis in chronic glomerulonephritis resolves itself into two main questions: (1) The possibility of complete recovery and (2) the probable expectation of life.

The severity of the initial acute attack is not always an accurate index of the subsequent course: severe acute attacks may be followed by complete recovery within a few months while cases setting in insidiously may develop into severe chronic glomerulonephritis which proves fatal within months or a few years.

During the first year after the onset of glomerulonephritis recovery is *possible* even in extremely severe cases. However, when there is continued impairment of renal function and hypertension increases, recovery is improbable after even a few months. In general, those cases in which edema is the outstanding manifestation during the first months have a better chance for recovery or at least a protracted course than those in which hypertension persists for as much as two months. It is the cases in which hypertension lasts for more than a few weeks that tend to rapid deterioration of renal function; hypertension after the first weeks is of ill prognostic omen. After glomerulonephritis is present for more than a year, no matter how mild its manifestations, complete recovery is very dubious, and this scarcely occurs after two years. An exception is possibly constituted by those cases which remain with only proteinuria but no impairment of renal function, hypertension or edema following the acute attack; some such residual proteinurias persist for decades without developing other evidences of chronic glomerulonephritis. It is possible that in some of these cases the proteinuria ultimately disappears. But in others after twenty years or more of nothing but proteinuria, impairment of renal function and hypertension appear and the patient succumbs to uremia.

By far the most important single factor in determining the duration of life in glomerulonephritis is the rate at which deterioration of renal function progresses. The tempo of the process varies greatly from case to case. In rare instances the fatal impairment of renal function with uremia develops within weeks, in another group it takes months, while in still others renal failure occurs only after decades. I have seen cases in which the duration of chronic glomerulonephritis ultimately terminating in uremia was over thirty years.

The rate of progress of injury to the kidney usually cannot be estimated from a single examination it is necessary to follow the case over a period of time the longer the better to learn if renal function is deteriorating. Up to the point of isosthenuria the *most useful* index for following the progress of renal damage is I believe the specific gravity test. In progressive cases a more or less rapid decrease in the maximum attainable specific gravity of the urine is noted although as a rule the downward progress is not continuous. After isosthenuria (maximum specific gravity about 1 010) is reached the specific gravity is no longer of help and the state of renal function is best judged by the blood urea nitrogen and urea clearance.

Some patients with hyposthenuria due to chronic glomerulonephritis retain their working capacity for years even ten or more. The same is true of those with moderate hypertension or recurrent slight edema. However such individuals are always in danger. Among the causes of aggravation of previously impaired renal function are intercurrent infections of the throat and respiratory tract although this danger is not as great as before antibiotics and pregnancy. The woman with chronic glomerulonephritis becomes pregnant only with much risk (*cf* Chapter 37). In the cases in which hypertension is present for years without great impairment of renal function death from cardiac failure or an independent cause may terminate the disease before its natural ending which is renal insufficiency with consequent uremia.

Generally speaking the higher the *blood pressure* the worse the prognosis. When the diastolic pressure is persistently above 120 mm entry into the malignant phase with hypertensive retinopathy and rapidly progressive renal insufficiency is usually not more than a year or two away.

The appearance of hypertensive retinopathy is of very bad prognostic significance the patient usually succumbs in less than two years advent of the retinal changes most often in less than a year. As in the malignant phase of essential hypertension the development of papilledema is usually soon followed by rapid deterioration of renal function and or hypertensive encephalopathy due to edema of the brain.

Epileptiform convulsions and other manifestations of hypertensive encephalopathy are of much graver prognostic significance in chronic than in acute glomerulonephritis. Death may occur during the seizure or within a relatively short period thereafter. However this is not always true as illustrated by the patient studied by Oppenheimer[32] and the writer who had dozens of severe convulsive seizures during a period of three years.

Patients with the nephrotic type of chronic glomerulonephritic usually do not survive more than a year or two after the appearance of edema. However there are exceptions who get along for several years and these from present indications are more common since ACTH and cortisone have been used in the treatment of the nephrotic syndrome. I have not seen any instance of the nephrotic syndrome which the history or other evidence indicated clearly to be due to chronic glomerulonephritis in which recovery occurred. Patients with the nephrotic type of chronic glomerulonephritis formerly often succumbed to intercurrent infections but this is rare since the introduction of antibiotics

Once renal decompensation with nitrogen retention in the blood appears in chronic glomerulonephritis only a minority of the patients survive more than two years. However, in exceptional cases, especially with careful dietetic management the patient may get along quite well and with some working capacity for several years. The prognosis is, of course, worse if nitrogen retention appears while the patient is on a low protein diet than if it is found when the diet has been unrestricted. There are unusual cases of outspokenly recurrent type in which azotemia accompanies the acute exacerbations to disappear with their subsidence. Also, although this is uncommon in chronic glomerulonephritis, nitrogen retention due to a combination of impaired renal function and well marked cardiac failure may clear up on bed rest and other treatment for cardiac insufficiency.

When well-marked uremic symptoms—nausea, vomiting, diarrhea, mental torpor, delirium, uremic eruptions, pericarditis, etc.—appear it is rare for the patient to improve even temporarily. But even here surprises occur on rare occasions even patients with uremic pericarditis improve enough to leave the hospital although the respite proves only temporary.

TREATMENT OF CHRONIC GLOMERULONEPHRITIS

Treatment during the first year of glomerulonephritis has already been outlined. The treatment of acute exacerbations of chronic glomerulonephritis does not differ essentially from that of the initial attack except that bed rest is often not enforced for as long a period in the effort to favor complete *restitutio ad integrum* which at this stage is highly improbable or impossible.

The Diet.—Opposing indications often conflict with one another in the selection of the diet in chronic glomerulonephritis. Excretory insufficiency calls for protein restriction while massive proteinuria and the nephrotic syndrome indicate an ample protein intake. The difficulties arise when both these indications co-exist in the same patient.

Little dietary restriction is called for in the asymptomatic stages of chronic glomerulonephritis with no edema, modest proteinuria, good excretory function, normal plasma proteins and at most slight hypertension. There is no evidence that in such cases restriction of protein slows the progress of the renal lesions or that such effect as very rigid salt restriction may have on the blood pressure (less will certainly have no effect) is worth the requisite interference with the patient's way of life. The asymptomatic stage of chronic glomerulonephritis often lasts for several years and may endure for decades; the evidence is lacking to justify the imposition of permanent dietary invalidism on such individuals who feel well, contribute useful activity and enjoy life. The writer not rarely encounters patients who have been put on stringent diets merely because proteinuria has been found in an insurance examination. It will be seen (Chapter 25) that there is no convincing evidence that the end products derived from the usual amount of protein in the diet in any way injure the kidney or accelerate the downward course or renal damage already present. Keutmann and McCann[80] fed 4 patients with chronic glomerulonephritis with hematuria between 40 and 200 grams of protein daily over a protracted period

hematuria diminished, renal function improved and the general condition of the patients improved during the period of the liberal protein ration. There is no reason why such patients with good excretory function should not have meat once daily and considerable latitude in the choice of other protein foods. On the other hand, except in the cases of the nephrotic type of glomerulonephritis with massive proteinuria, there is also no reason why especially large quantities of protein should be eaten. Even active people can get along with a daily ration of 1 gram of protein per kilogram body weight. A diet containing this amount of protein can be made palatable over years even for individuals who have always been meat eaters. Many patients with chronic glomerulonephritis have been so inculcated with the fear of meat and other protein foods that it is difficult to persuade them to eat sufficient protein and any untoward symptoms that appear are blamed on the much maligned meat. It is not uncommon in patients with chronic glomerulonephritis who have been kept on an inadequate ration of protein for a long time despite good renal function to observe improvement in bodily vigor and anemia quickly after the institution of a diet containing adequate nitrogenous foods. In some such cases, notably those with hypertension and proteinuria but tolerably good excretory function, the fear of the patient for protein foods other than milk is one of the greatest difficulties with which the physician has to contend.

Very different is the dietetic indication in chronic glomerulonephritis if the concentration test, the blood urea or the urea clearance disclose marked impairment of excretory function. The protein intake should than be restricted and every effort made to keep endogenous protein breakdown as low as possible by a high carbohydrate and fat intake. Further details of the low protein high calory diet will be found in Chapter 7.

An indication for considerable quantities of protein in the diet is furnished by the nephrotic type of glomerulonephritis, i.e., the type of case with massive proteinuria, tendency to edema, tolerably good excretory function and usually but moderate or no hypertension. In such cases sufficient protein should be given to cover the loss of protein in the urine as well as the metabolic requirements and in addition to repair the protein starvation which has usually developed before the start of dietetic treatment. Under such circumstances the requisite daily protein ration for at least a period of weeks or even months may be over 100 grams. Such a diet is not uncommonly followed by lessening or even disappearance of edema. But before giving so much protein one must be sure that excretory function is adequate: the patient should be able to concentrate the urine above a specific gravity of 1.020 and the blood urea should be within normal limits. Details as to the technique of the high protein diet will be found in Chapter 16.

Fluid intake is to be regulated in accord with the functional capacity of the kidney. If renal excretory function is good, there is no need for any other regulation of water consumption than the thirst of the patient. But hyposthenuria calls for high water intake, for polyuria is the only mechanism open for maintenance of excretion. The high fluid intake is usually aided by the spontaneous thirst of hyposthenuric patients. In such cases with azotemia increase in fluid intake often results in decrease in

blood urea Unless the patient has been previously dehydrated, or the weather is very hot, nothing is to be gained by increasing the water allowance above 2500 or 3000 cc daily Heart failure is not a contraindication to raising the fluid allowance

Sodium restriction is indicated in patients with edema, as well as in those in whom massive proteinuria and/or hypoproteinemia indicate liability to fluid retention Marked hypertension also calls for sodium restriction In patients with the nephrotic form of glomerulonephritis tubular function is usually adequate to permit dietary sodium restriction to levels as low as 500 mg per day without great danger of sodium depletion though even here it must be watched for But when there is hyposthenuria with or without azotemia, sodium restriction is to be carried out only with much circumspection because of the danger of salt depletion If the syndrome of salt-losing nephritis (page 622) appears which is rare in glomerulonephritis, a high salt ration may be used

It is rare for patients with chronic glomerulonephritis contrary to those with the Kimmelstiel-Wilson syndrome or essential hypertension to become obese But if obesity (not edema) does appear on the low protein, high calory diet the caloric intake should be lowered

Medicinal Treatment —No medicinal agents have been demonstrated to alleviate or retard the progress of the lesions in the kidneys There is no evidence that antihistaminics antibiotics cortisone or ACTH specifically affects glomerulitis

Notwithstanding the fact that ACTH and cortisone have not been shown to alter the progression of the glomerular lesions they have proved the most valuable therapeutic agents available in many instances of the nephrotic syndrome due to chronic glomerulonephritis The cases in which they are most apt to prove of help are those in which the nephrotic syndrome occurs in the presence of tolerably good excretory function normal blood urea and little or no hypertension In such instances of the nephrotic type of chronic glomerulonephritis ACTH and cortisone may produce results similar to those obtained in chronic nephrosis diuresis evacuation of edema repair of hypoalbuminemia and decrease in lipemia (*cf* Chapter 16) However worthwhile results from ACTH and cortisone are not as frequent in the nephrotic form of glomerulonephritis as in chronic nephrosis and they are usually even more transitory When the nephrotic syndrome is accompanied by azotemia or marked hypertension significant diuresis is even less frequent and untoward and even dangerous side effects are not as rare I have several times seen aggravation of hypertension by ACTH and once threatening pulmonary edema developed Azotemia may be markedly aggravated For these reasons I have not recently used ACTH or cortisone for the treatment of chronic glomerulonephritis when there is azotemia or more than minimal hypertension Details of the administration of ACTH and cortisone will be found on page 490

Diuretics have a limited sphere of usefulness in chronic glomerulonephritis and are rarely long continued Theophyllin and other xanthines alone are valueless Urea or ammonium chloride sometimes produce modest diuresis but it is rarely significant these diuretics should not be used if excretory function is impaired and they are rarely long continued

Exceptionally mercurials produce profuse diuresis but more often they fail and if there is initial success the good result is rarely repeated many times. The mercurials should not be used when there is hematuria or marked impairment of renal function with azotemia; the hematuria may be aggravated and with severely impaired renal function there is danger of toxic effects. Salt poor albumin will often produce transitory diuresis but rarely proves worth the considerable expense. Further details regarding these and other diuretics will be found in Chapters 6 and 16.

Since nitrogen mustard inhibits certain antigen antibody reactions including experimental glomerulonephritis, Chasis[51] and his associates have administered the drug to patients with chronic glomerulonephritis (2 doses of 0.2 mg./kg. on successive or alternate days). In some of the patients diuresis occurred, edema was evacuated, proteinuria diminished and the filtration rate increased. Kelley and Panos[57] obtained diuresis with nitrogen mustard in 8 of 9 children with the nephrotic syndrome but there was no consistent effect on proteinuria. Apparently the results of treatment with nitrogen mustard, with which the writer has insignificant personal experience, are usually temporary. Because of the possible side effects of nitrogen mustard its use is to be regarded as still in an investigative stage.

In many cases of chronic glomerulonephritis *anemia* becomes a prominent or even the dominant manifestation for months or even years. The anemia may appear with only modest azotemia, e.g. 50 mg. urea nitrogen per 100 cc. blood. Unfortunately the characteristic normochromic anemia of azotemic patients does *not* respond to iron, liver, folic acid or vitamin B_{12}. Transfusion of red blood cells is the only therapeutic remedy of value. Whole blood is to be given if there is no evidence of heart failure, otherwise packed red cells because of the danger of provoking left ventricular failure in these usually hypertensive individuals. In some patients with chronic glomerulonephritis protracted protein restriction contributes to the genesis of edema; in these *increase* in the protein ration may be of help. If there are no symptoms of clearly anemic origin, transfusions should not be started in chronic glomerulonephritis unless the hemoglobin falls below 9 grams. Some patients require 25 or more transfusions over a period of a year or two.

If heart failure develops digitalis is called for. Leil and Steuer[82] found that the amount of digitalis necessary to produce clinical and electrocardiographic evidences of digitalization or symptoms of intoxication is not lessened by renal insufficiency. However since it has been possible to gauge dosage somewhat more accurately by the use of pure glycosides it has seemed to me that the maintenance dose of digitalis preparations is less in the presence of renal damage severe enough to produce even slight azotemia. This is hardly surprising. Okita[83] *et al* have shown that 60 to 80 per cent of a dose of radioactive digitoxin administered to a patient with heart failure is eliminated through the kidneys. Especial care must be taken to avoid overdigitalization in renal insufficiency because it may be difficult to decide whether nausea and vomiting are due to overdosage or uremia. In the prescription of salt restriction and mercurial diuretics

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Sufferers from glomerulonephritis who are ambulatory should be particularly careful to avoid contact with individuals having a sore throat or other infection. Every effort should be made to avoid exposure to inclement weather because of the danger of sore throat, etc.

There is no objection to the use in moderation of alcohol, tobacco, coffee or tea. What is said on the use of these sources of pleasure in essential hypertension (Chapter 28) applies equally in glomerulonephritis. Patients with marked hypertension are to be cautioned regarding sexual excess because of the danger of pulmonary edema, which is greater in those having even slight peripheral edema.

Moderate exercise, preferably walking or not too much golf when the weather is good, should be encouraged in patients whose cardiac reserve is adequate. Strenuous exertion is to be avoided; even healthy people often have protein and sometimes red cells in the urine after violent exertion. Injunctions in this regard are particularly necessary in children, although the psychological aspects of restraint must be borne in mind. Sea bathing with its rapid fluctuations in skin temperature is best interdicted in patients with any evidences of activity of the nephritic process; it will be recalled that red cells are often found in the urine after sea bathing. However, basking in the sun on the beach is to be encouraged.

An occupation is preferable, if at all possible, which does not involve hard physical work or exposure to cold and wet. The question of future occupation often arises in youths with proteinuria but no other manifestations and may be difficult to decide. Positions in offices or as salesmen or teachers are examples of well-suited occupations. One must never give advice regarding occupation which it is economically impossible for the patient to follow; psychologic trauma is then added to the physical difficulties.

The question of pregnancy is discussed in Chapter 32.

Climatic Treatment.—For the well-to-do it may be well to spend the winter months in Florida, Southern California or some other warm climate. One of the principal advantages is lesser incidence of respiratory infections. But bed-ridden patients should not be sent to distant localities, for them there is no advantage in the change in climate. There is no evidence that any of the spas which are reputed to help patients with renal disease are of avail in glomerulonephritis. In fact, drinking large quantities of sodium-containing waters, which is often part of the regimen, may be distinctly harmful.

The question often arises whether an individual in an asymptomatic stage of chronic glomerulonephritis should permanently change his residence to, or enter college in, a warm climate. Careful consideration should be given to economic and social factors before giving advice in this regard.

It is important that climatic treatment should not be suggested to an individual who cannot afford it; the benefits to be anticipated are not sufficient to warrant the great financial sacrifices which such patients sometimes make to attain them.

for heart failure in glomerulonephritis, the state of renal function must be borne in mind so as to avoid the danger of salt depletion

Treatment of Infectious Foci —Patients with glomerulonephritis should be examined for infectious foci If an infection is found and may be helped by an antibiotic it should be given Should infected tonsils, teeth or sinuses be found which would require surgical treatment in the absence of glomerulonephritis this should be done In general it is well to postpone operative intervention until acute manifestations have cleared up, for tonsillectomy and other operations on infected foci are occasionally followed by exacerbation of symptoms Thus, Page and Alving[84] found by means of the urea clearance, that renal function was depressed in the days immediately following the operation in 3 of 31 nephritics who underwent removal of tonsils adenoids or teeth, in 1 advanced case uremic symptoms were precipitated There was also often increase in hematuria and cylindruria for some days after operation As a rule little or no benefit is seen after such procedures, and one should be careful not to exalt unduly the hopes of the patient or his family with regard to the results of removal of tonsils or teeth Observations of improvement of the nephrotic syndrome in children following surgical or other drainage of an infected paranasal sinus have been mentioned (page 454) but I have not had similar good fortune There can be little doubt that removal of foci was long overdone particularly the puncture of sinuses has been carried out too often It is rarely necessary since the introduction of penicillin I am not sure that I have seen improvement in glomerulonephritis unequivocally due to surgical treatment of an infected focus

Physiotherapy —Sweating procedures and various types of baths are often used in glomerulonephritis particularly in European spas Bronner and Schueller[85] advocated diathermy in chronic nephritis There is no reason to think that any of these procedures help other than through suggestion

Surgical Treatment —Edebohls[86] and others claimed improvement and even cure of chronic glomerulonephritis from decapsulation Such an operation comes into consideration only during acute exacerbations with extreme oliguria or anuria and the remarks made in the chapter on Acute Glomerulonephritis apply equally to the acute phases of the chronic disease I have never recommended the operation in chronic glomerulonephritis

General Management —Patients who feel well enough to be up and about should be allowed to do so unless they have heart failure are in an acute exacerbation with hematuria or have an intercurrent infection Edematous patients seem to do about as well when up and about as when bed rest is enforced, moderate increase in the edema of the legs as a result of leaving bed is not harmful The same is true of such symptoms as proteinuria the presence of small or moderate numbers of red cells in the sediment hypertension and impairment of renal function if they seem to be stationary, the patient may be allowed to get about Many patients carry on an occupation for years despite slight edema that comes and goes proteinuria and microscopic hematuria

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In many of the cryptogenic cases in adult females who have had children it is probable that the original acute pyelonephritis dates back to pregnancy and that dilatation of the ureter and urinary stasis secondary to pressure by the pregnant uterus predisposed to the infection There is experimental evidence that urinary stasis favors the implantation of circulating bacteria in the kidneys Seemingly primary chronic pyelonephritis is much more common in females than in males among 96 cases of pyelonephritic contracted kidney studied at necropsy by Raaschou[7] 55 per cent of the females and 36 per cent of the males revealed no primary lesion The predominance of females in the totality of cases of pyelonephritis applies to children and up to the fifth decade after that prostatic enlargement becomes significant and there is no great sex predominance In Nesbit and Cooper's[8] 172 cases of chronic pyelonephritis the etiology was not evident in 99 of the cases with known etiology the most frequent in the female was pregnancy and in the male lower urinary infections and prostatism There may be a form of chronic pyelonephritis with famial predisposition for Perkoff[9] *et al* have described a family in which 44 of 134 members were affected

The colon bacillus is the organism most often cultured from the urine but there are also many cases due to aerobic and anaerobic streptococci staphylococci Aerobacter aerogenes proteus pyocyaneus and other bacteria In the obstructive cases mixed infections are common Wilhelm's[10] detailed studies of the bacteriology of chronic pyelonephritis have revealed that especially in the obstructive cases there has been a change in the organisms found in the urinary cultures since the introduction of potent antibacterial agents in that the less susceptible bacteria have become much more common He found that Aerobacter aerogenes has been especially frequent and there is also a considerable incidence of pyocyaneus infections In interpreting urinary cultures especially for the differential diagnosis between pyelonephritis and glomerulonephritis it should be borne in mind that bladder urine from healthy persons may reveal organisms (Schulte[12] Slotkin[13]) Schulte found that urine obtained from the bladder through the cystoscope often affords positive cultures but this is not true of the renal pelvis

Pathological Anatomy —The disease may be bilateral or a little less often unilateral In the kidney involved by chronic pyelonephritis one almost invariably encounters an admixture of acute and chronic inflammatory processes and the scarring in which healing terminates In very long standing cases evidences of active inflammation may be scanty Most often the histological picture is that of a recurrent inflammatory process which has passed through repeated phases of healing and exacerbation

The process is rarely symmetrical on both sides the differences between the two kidneys are usually much more pronounced than in glomerulonephritis and there are completely unilateral cases Sometimes the diagnosis of chronic pyelonephritis can be made with confidence from the gross appearance but often differentiation from glomerulonephritis the arteriolosclerotic kidney or multiple healed infarcts requires microscopic examination The kidneys vary in size from normal or even slightly enlarged to extremely small organs One kidney may be so small that such an organ has been confused with congenital hypoplasia (*cf* Emmett[12] *et al*) The

Chapter

22

CHRONIC PYELONEPHRITIS

ONLY in the past two decades has the profession become cognizant of the great frequency and importance of chronic pyelonephritis. Indeed if both the acute and chronic stages of pyelonephritis are included, it is doubtless much the most frequent of kidney diseases. Of 93 cases with uremia coming to necropsy, 32 were due to pyelonephritis (Lakely[1] *et al.*). At necropsy one very often sees scars in the kidneys which are due to healed pyelonephritis, although there is no history of the disease. For many years the acute illness characterized by pyuria, fever and chills was diagnosed as "acute pyelitis," but the studies of Wilson and Schloss[2] and others showed that they are actually pyelonephritis. The pathological anatomy was described many years ago by Wagner[3] and in detail by Loehlein,[4] and urologists have long been familiar with the renal changes secondary to obstruction and infection of the urinary passages. However, it is only since the publications of Longcope[5] and Weiss and Parker[6] that internists have appreciated how frequently, in the absence of obstruction or infection of the lower urinary tract, chronic bacterial infections of the kidneys produce clinical pictures characterized by impairment of renal function and hypertension, and frequently terminating in uremia. There can be no doubt that in the past many cases of pyelonephritis have passed for glomerulonephritis. At present, in New York City at least, chronic pyelonephritis is a much more frequent cause of uremia than is glomerulonephritis. The disease contributes a substantial moiety of the totality of cases of malignant hypertension.

The term pyelonephritis designates an inflammation of bacterial etiology which takes its renal origin in the mucous membrane of the pelvis and/or the interstitial tissue of the kidney. Implication of the tubules and glomeruli is secondary. In a high proportion of the cases the renal point of departure is obviously the pelvis; how many take origin in the intertubular tissue of the kidney remains to be demonstrated but this may well be the pathogenesis in most of the cases. The organisms may reach the kidney by ascending infection within the ureters or by the blood stream; while infection via the periureteral lymphatics has been suggested, it has not been established.

Etiology and Pathogenesis.—There are two great groups of cases: Those in which pyelonephritis is secondary to infection or obstruction of the urinary passages, and those in which neither clinically nor anatomically is the source of the renal infection demonstrable and there is every reason to believe that the bacteria reached the kidneys via the blood stream.



Fig 34 – Section of the kidney of Fig 33 under the low power the dilated tubules containing casts look like thyroid tissue



Fig 35 – Higher power of 33 showing dilated tubules interstitial cellular infiltration and a thickened small artery

capsule is often thickened and strips with difficulty, taking with it bits of kidney tissue The surface of the kidney is usually irregularly pitted and granulated with depressed scars and nodular elevations composed of normal or hyperplastic tissue The granulation is generally much more uneven than that of glomerulonephritis or arteriolosclerosis Rather broad and shallow depressions are common On section the cortex is irregularly narrowed in the cases with contraction The patchy distribution of the process is evident in the cut section The pelvic lining is reddened, covered with exudate, or pearly-white and thickened depending on the stage of the process at the time of nephrectomy or death If there was urinary obstruction it is documented by dilatation of the pelvis and calyces However in most of the cases not secondary to disease of the urinary tract, and presumably of hematogenous origin the pelvis is not enlarged and may



Fig 33 —Chronic pyelonephritis of about five years duration with continuous pyuria recurrent febrile episodes and final uremia There were no changes in the urinary passages

be much shrunken In cases which have succumbed during an acute exacerbation abscesses may be present

Histologically a variegated picture is seen which usually is the resultant of repeated episodes of interstitial inflammation and healing Except with extreme contraction the process is patchy Most striking at first glance are usually extensive cellular infiltrations and areas of dilated tubules containing large casts and lined by flattened epithelium Tiny vestiges of atrophic tubules are interspersed The interstitial infiltrates are usually composed almost entirely of lymphocytes and plasma cells but large numbers of polymorphonuclear leucocytes may bear witness to an acute exacerbation The tubules may then contain pus Areas of fibrous connective tissue are present in long-standing cases Periglomerular fibrosis is often prominent and a smaller or larger proportion of the tufts shows

hypertension In many instances of pyelonephritis with profuse pyuria the sediment contains few or almost no red cells or casts But episodes of gross hematuria may occur and only cystoscopic examination may reveal whether the blood comes from hemorrhagic cystitis or pyelitis With renal insufficiency large granular and waxy casts may be numerous

Proteinuria varies greatly Usually the urine does not contain more than a trace to one or two grams daily However there may be several times as much this has been a source of confusion with glomerulonephritis * In the pyelonephritic contracted kidney as well as during periods when the inflammatory process is quiescent proteinuria may be minimal and even absent at times

Bacteria may be demonstrable in the urine by culture and stainable in the sediment B coli is the most common organism but a large variety of others may be found and there may be mixed infection For long periods bacteriuria may not be demonstsable despite the presence of pus in the urine The *reaction* of the urine is influenced by both bacteriuria and impairment of renal function as well as by therapeutic measures When *colon bacilli* are present in the urine it is usually acid while proteus infections may result in alkaline urine Longcope pointed out that with renal insufficiency the urine though sterile may be neutral or slightly alkaline in the presence of low CO_2 combining power of the blood

Renal Function —Pyuria may be present for years before renal function becomes sensibly impaired However sooner or later this generally occurs and is documented by hyposthenuria decreased urea clearance and phenolsulphonphthalein excretion and ultimately azotemia Often the disease is not detected until the patient is uremic she may state that she felt well until a short time before The progress of the renal insufficiency is often remarkably slow almost as slow as in polycystic disease patients may have azotemia for more than five years and yet be active Deterioration and improvement in renal function may be correlated with appearance and subsidence of acute febrile exacerbations Renal function in chronic pyelonephritis has been studied in great detail with modern methods by Raaschou He found that renal blood flow (diodrast clearance) glomerular filtration (inulin clearance) and tubular secretory capacity (diodrast Tm) are all depressed when renal function is impaired As would be anticipated from the variegated anatomical findings the pattern of impairment of renal function is inconstant However in moderately and far advanced cases Raaschou's observations indicate a tendency to impairment of tubular function disproportionately more severe than the damage to glomerular filtration he observed in many cases that diodrast Tm is depressed more than is inulin clearance The excellent study of Nussbaum[14] and his as-

* Not extremely rarely patients with prostatism or less than three years after prosta
te tomy present themselves complaining of swelling and weakness Their clinical pic
ture is compounded of edema massive proteinuria hypoalbuminemia impairment of
renal function and usually hypertension The impairment of renal function is progres-
sive and the end is usually uremia The urine generally contains only modest numbers
of white cells and perhaps a few clump Whether the renal mischief originates in
ascending pyelonephritis or has other pathogenesis remains to be established But the
number of such nephrotic syndromes I have seen in prostatics is too large to be for
tuitous

varying stages of hyalinization, fibrosis and atrophy Individual glomeruli may be the site of a glomerulitis indicated by increase in the number of nuclei Almost always, however, there are some normal glomeruli The small arteries in involved areas are often the seat of endarteritis similar to that seen in glomerulonephritis (page 601) Hyalinization of the afferent arterioles may be present If the hypertension has entered the malignant phase, arteriolar necrosis may be present and with it necrotic glomeruli The wall of the pelvis is usually thickened and the site of cellular infiltration The capsule likewise shows perinephritis

Clinical Picture —When chronic pyelonephritis complicates urolithiasis prostatism, neurogenic bladder or another lesion of the urinary tract which is still present, the clinical picture is a composite of the symptomatology emanating from the original and the renal affection In other cases there is a history of acute pyelonephritis during childhood or during pregnancy or of lower urinary tract disease, but this was followed by a period of years during which the patient regarded herself as well or may have known of asymptomatic pyuria In still other cases and these are the ones which come most often initially in the purview of the internist, the disease apparently arises *de novo* with no evidence to show whether it resulted from hematogenous or ascending infection Some of the patients have a long history of weakness inability to gain weight 'anemia' which may be real or merely a sallow complexion albumin in the urine, recurrent fever and chills regarded as colds backache, abdominal pains (cases of pyelonephritis have undergone laparotomy) or other symptomatology the relationship of which to pyelonephritis passed undetected There may have been recurrences of pyelonephritis during successive pregnancies with complete well-being in the intervals Some of the patients have been known to have pyuria for years but have felt entirely well It is not very rare for the patient first to come under clinical observation when already uremic in such cases the urine may contain only a few white cells and the case may be interpreted as glomerulonephritis until the post mortem examination Formerly there were cases of pyelonephritis which went continuously downhill and succumbed to renal insufficiency in less than a year but these hardly occur now with the improvement in antibacterial therapy

Fever and *chills* are present in the history of many of the patients Usually these have been regarded as colds Low grade fever may persist for months, sometimes with exacerbations of higher pyrexia of septic type In other cases, however there is no history of febrile episodes and the temperature is not significantly elevated under observation

The Urine —Pyuria is the classical sign of pyelonephritis The patients may have cloudy urine for years or decades augmented during acute exacerbations According to Lippman [13] while the normal excretion of white and epithelial cells is less than one million in 24 hours in chronic pyelonephritis the number may range from 30 million upwards However the disease may pass through stages in which the inflammatory process is quiescent or extinguished (healed stage of Weiss and Parker) and the urine is clear with few leucocytes in the sediment This is especially apt to occur in long standing cases in which the clinical picture is dominated by

The face may be slightly puffy but marked edema is rare and usually has a cardiac component in its pathogenesis. The combination of proteinuria, even modest, and anorexia often results in hypoalbuminemia; the globulin content of the serum is usually increased, presumably partly as a result of the infection. In children chronic pyelonephritis may be associated with renal osteodystrophy (page 626). With azotemia anemia develops. The infection may result in moderate leucocytosis and the sedimentation rate may be accelerated.

Pyelographic Findings.—The intravenous pyelogram of course affords a valuable index of renal excretory function. The contour of the pyelogram may or may not be altered in chronic pyelonephritis. Nesbit and Conger observed a normal pyelogram in 22.6 per cent, minimal changes in 54.7 per cent, moderate changes in 15 per cent, and marked changes in 7.5 per cent of 159 cases of chronic pyelonephritis. The changes consist in various dilatations, constrictions or distortions of the pelvis and ureters. In the hematogenous cases the pelvis is most often decreased in size. There may be diminution in the size of the renal shadows. In the cases not secondary to disease of the urinary passages cystoscopy usually reveals little change in the bladder.

Prognosis.—Chronic pyelonephritis is usually a disease of many spontaneous exacerbations and remissions. Even when the urine has been sterile on repeated cultures and the centrifuged sediment reveals few white cells the danger of recurrence is always present. Many patients feel entirely well and are able to look after their household for ten or twenty years despite pyuria. The development of renal insufficiency or hypertension usually signals the last stage of the disease. However, as mentioned above, the progress of impairment of renal function is often extraordinarily slow in chronic pyelonephritis and the patient may be active for several years with moderate azotemia. The hypertension not rarely goes into the malignant phase, in which event the course is usually rapidly downhill with death in less than two years after the retinal lesions have appeared. When pyelonephritis is secondary to some such lesion of the urinary passages as urolithiasis, prostatic enlargement or stricture of the urethra, removal of the obstruction may be followed by clearing of the renal disease. Unfortunately this is not always the case; not rarely pyuria persists after prostatectomy or other elimination of a causative lesion. Pyelonephritis of pregnancy most often clears up completely but not rarely persists as the chronic disease or recurs with succeeding pregnancies.

Statistics of the outcome of pyelonephritis vary widely, probably largely because of inclusion of cases of different causation. The proportion of patients recovering completely is much higher when pyelonephritis is secondary to such lesions of the urinary tract as urolithiasis or prostatic enlargement which can be removed than in the hematogenous cases first seen in the chronic stage. Braasch and Cathcart[18] found that one third of patients with pyelonephritis recover, one-third improve strikingly and the remainder progress. On the other hand, Nesbit and Conger had only 3 complete recoveries (disappearance of all symptoms, repeatedly negative urinary cultures) in 170 cases of pyelonephritis. Nowadays with improved antibacterial treatment the proportion of recoveries in chronic pyelo-

sociates has shown that chronic pyelonephritis may so impair sodium and chloride conservation by the tubules that a "salt-losing nephritis" results with a clinical picture simulating adrenocortical insufficiency.

Uremia.—As already mentioned, the initial complaints may be uremic. A considerable fraction of the patients ultimately succumbs to uremia. The progress of the renal insufficiency is usually very slow and punctuated by periods of improvement, either spontaneous or the result of treatment. Weiss and Parker even describe prolonged improvement after the development of uremic pericarditis; this I have not observed. The uremic manifestations do not differ from those in other forms of renal disease.

Hypertension.—It was pointed out by Longcope, Weiss and Parker and others that chronic pyelonephritis may cause high blood pressure. Bell[15] regards severe hypertension in chronic pyelonephritis as due to a complication, but this is diametrically contrary to my experience. It is true that hypertension does not occur in acute pyelonephritis, but it develops in a high proportion of cases of chronic pyelonephritis and in a majority of patients with pyelonephritic contracted kidney. Tremendous hypertension may occur in children with chronic pyelonephritis. Butler[16] found an average blood pressure of 190/140 mm. in 7 children between three and eleven years with chronic pyelonephritis. In these cases in children there can be no doubt that the hypertension results from the pyelonephritis. Braasch and Jacobson[17] found that in patients with chronic pyelonephritis under the age of fifty hypertension is twice as frequent as in controls. The hypertension may be of the utmost severity and enter the malignant phase with resultant retinopathy, encephalopathy and renal arteriolar necrosis. While necropsy may reveal hyalinization of the renal arterioles and endarteritis of the small renal arteries in chronic pyelonephritis with hypertension, this is not always the case (Longcope, Weiss and Parker, own observations). Such observations show that chronic pyelonephritis, like glomerulonephritis, may cause hypertension without the intermediacy of arterial or arteriolar lesions. Hypertension may result from unilateral pyelonephritis (see below).

Heart failure may develop in patients with chronic pyelonephritis and hypertension. While major coronary thrombosis or cerebrovascular accidents may complicate pyelonephritic hypertension, this has been decidedly uncommon in my experience.

Local Symptoms.—Pains in the loins or flanks are very common and are sometimes accompanied by percussion tenderness. Many patients with pyelonephritis have for years attributed their backache to lumbago, gynecologic conditions, etc. Abdominal pains are not very rare and such patients have undergone laparotomy. Dysuria and other symptoms of cystitis are often initial manifestations and may occur at any time of the disease.

General Manifestations.—The general health may remain excellent for years despite constant pyuria. But weakness, anorexia and emaciation may appear even before there is azotemia and are usually accelerated after the latter appears, although there are surprising exceptions in which patients are able to work with few complaints despite moderate nitrogen retention. With hyposthenuria the skin usually becomes dry and inelastic

Hg/10 mm A second similar case was included in Butler's pioneer communication Butler's paper awakened great interest in the subject of hypertension due to unilateral kidney disease and many cases were published of variegated etiology (pyelonephritis of calculous or other etiology hydronephrosis narrowing or occlusion of the renal artery renal tuberculosis perinephritis Wilms tumor etc) Unilateral renal disease was assiduously sought for in patients with seeming essential hypertension A great many unilateral nephrectomies were performed with the object of alleviating hypertensive disease However the proportion of cases in which nephrectomy relieved hypertensive disease was so small that doubts were cast on the causal relations between unilateral renal disease and hypertension (cf Bell[14]) The subject is reviewed in detail by Smith[9] While he concludes that the bulk of urologic disease does not cause hypertension he accepts 47 cases in the literature as having fulfilled acceptable criteria that elevated blood pressure was reduced to normal levels (140 90 mm or below) for at least one year after unilateral nephrectomy

The writer does not doubt that unilateral pyelonephritis or other unilateral renal disease *sometimes* produces high blood pressure I have seen at least 2 cases (calculous pyelonephritis arteriosclerotic and thrombotic narrowing of a renal artery) in which unilateral nephrectomy was followed by reduction of chronically elevated blood pressure to normal Embolism of one renal artery may produce hypertension (page 311) When extreme hypertension complicates unilateral pyelonephritis in a young child there would seem to be no room for reasonable doubt that the pyelonephritis is the cause of the high blood pressure Completely obscure is the reason why high blood pressure occurs in some instances of unilateral pyelonephritis and is absent in the larger moiety However the fact that some patients with glomerulonephritis do not have high blood pressure causes no one to doubt that glomerulonephritis can elevate the blood pressure The finding that unilateral nephrectomy in a patient with unilateral kidney disease has no effect on hypertension does not prove that the hypertension was not originally the result of the unilateral renal lesion There are observations in rabbits with hypertension due to constriction of one renal artery that if the kidney with impaired circulation is removed after a sufficiently long interval the hypertension still persists (page 329) Whatever the explanation of failure of unilateral nephrectomy to cure hypertension may be it is not necessarily disease of the other kidney This is indicated by the interesting study of Weiss and Chasis[21] on a patient with hypertension and unilateral renal disease Following nephrectomy which failed to affect the blood pressure they found that the remaining kidney showed *supernormal* blood flow glomerular filtration and tubular secretion

Unilateral nephrectomy for the treatment of hypertensive disease was greatly overdone in the first years after Butler's paper It should be carried out only after the most careful consideration There should be no evidence of disease of the other kidney the function of which should be faultless And the function of the affected kidney should be absent or insignificant For the proportion of even meticulously selected cases in which unilateral nephrectomy abolishes hypertension is small and with persistent hypertension one is in no position to sacrifice even a small

nephritis is much higher. Such recoveries, however, occur almost solely among the cases treated before the onset of significant impairment of renal function or hypertension. When these manifestations are present, while pyuria and bacteriuria may be suppressed, though they often recur, the renal damage progresses and most of the patients ultimately succumb to uremia or less often the consequences of hypertension. However, the course is often protracted for many years. Raaschou found that about one-third of patients with pyelonephritis succumb to uremia and about one-sixth to consequences of arterial hypertension. Chronic pyelonephritis usually lasts so many years that many of the cases fall victim to unrelated disorders.

Treatment.—Several lines of treatment come into consideration in chronic pyelonephritis.

1. Every patient should receive careful urological study. If the renal lesion is secondary to urolithiasis, prostatic enlargement, infection of the lower genital or urinary tracts, congenital anomalies, etc., these should receive appropriate treatment. An acute exacerbation during pregnancy may call for ureteral catheterization.

2. The urine should be studied bacteriologically, both by culture and smear. If an organism is demonstrated, appropriate antibacterial treatment with antibiotics, sulfonamides and/or alteration of the reaction of the urine should be instituted. The nature of the antibacterial treatment is guided by tests of the sensitivity of the organism to the different agents.

The antibacterial treatment should be intensive and protracted in the effort completely to eliminate and not merely to suppress the infection. Unfortunately, this goal often can not be attained. Especially in the use of sulfonamides it should be borne in mind that when renal function is impaired the blood level may rise rapidly from very small doses (cf. Fishberg[19]). Likewise, with impaired renal function small amounts of ammonium chloride or mandelic acid derivatives may produce profound acidosis. Even if a pathogenic organism can not be demonstrated in the urine, antibacterial treatment should be administered if fever or pyuria indicate that infection is still present.

3. Impairment of renal function and uremia are to be managed as in other diseases (page 223). The same is true of heart failure, anemia and other manifestations.

4. The question of nephrectomy in unilateral pyelonephritis is discussed in the next section.

Hypertension Due to Unilateral Pyelonephritis.—Cases in which high blood pressure results from unilateral chronic pyelonephritis or other unilateral renal disease are of great interest not only from practical points of view but also because of their bearing on the pathogenesis of renal hypertension. The existence of such cases was first established by Butler.[16] His patient was a boy of seven years with a stone in the right ureter which was removed. At the time, the blood pressure was 98/50 mm. Right hydronephrosis was present and right pyelonephritis developed. The blood pressure rose as high as 168 mm. systolic and 110 mm. diastolic. Right nephrectomy was followed by return of the blood pressure to normal; in the twenty months after operation the blood pressure was never over

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amount of functioning kidney. Needless to say, the physician should take pains to make clear that the chances of helping hypertensive disease by unilateral nephrectomy are not great. But if one kidney is nonfunctioning and the other faultless, the risk of the operation is small, removal of the kidney constitutes no loss, and even a rather small possibility of help may be worthwhile. If nephrectomy is indicated on urological grounds, the presence of hypertension is not a contraindication.

In several series in the literature (*cf* Smith), the incidence of hypertension is not significantly greater in urologic disease than in controls. This, however, does not prove that urologic disease never participates in the pathogenesis of hypertension. The nature of renal hypertension is not elucidated (Chapter 10) and it may be that urologic disease may set in action mechanisms which counter as well as favor elevation in blood pressure. When urologic disease in young children is accompanied by such blood pressures as 220/150 mm there would seem to be no reasonable doubt of the connection.

Necrotizing Pyelonephritis in Diabetes Mellitus.—Infection of the urinary tract and pyelonephritis are more common in diabetics than in others. Baldwin and Root found that about 20 per cent of patients succumbing to diabetes have infections of the kidneys; the percentage is doubtless less now that antibiotics are available. Harrison and Bailey[3] were able to culture bacteria from the urine of diabetics more than six times as often as from controls. Urinary infection in the diabetic may be manifested merely by asymptomatic pyuria lasting months or years and often responding readily to antibacterial treatment though with marked tendency to recur. In unusual cases, however, severe pyelonephritis develops which may run a fulminant and rapidly fatal course due to either renal insufficiency with uremia or overwhelming infection. There may be septic fever, chills and bacteremia. Anatomical examination in fatal cases reveals suppurative and necrotizing pyelonephritis with thromboses in the small vessels. The necrosis is especially apt to involve the renal papillae. However, necrosis of the renal papillae is not a specifically diabetic lesion. Robbins[24] *et al* found that of 26 cases with necrotizing papillitis 7 were in nondiabetics. Experimentally, renal papillary necrosis has been produced in the rabbit by the combination of ureteral ligation and intravenous injection of bacteria (Mallory *et al.*) and in the dog by ureteral ligation alone (Muirhead *et al.*[6]).

According to Harrison and Bailey, necrosis of the renal papillae is manifested in the pyelogram by an irregular filling defect which strikingly resembles that in renal tuberculosis. In several cases the diagnosis of renal papillary necrosis has been made by examination of bits of tissue voided in the urine (Johnston[7]).

Fulminating pyelonephritis in diabetes seems to have become much rarer since the introduction of antibiotics. The cases probably can be largely prevented by antibacterial treatment of low grade urinary infections.

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from those of diffuse glomerulonephritis not only in their focal distribution but also in their causation nature prognosis and treatment Moreover it is to be emphasized that *independent* glomerular tubular and interstitial lesions are all usually present in such cases though any one may predominate in a given instance For these reasons the term *focal nephritis* will be used in this book

The differentiation of focal nephritis from glomerulonephritis is not universally accepted In studies on 301 cases of acute nephritis in children Payne and Illingworth[7] found no absolute distinguishing criterion between glomerulonephritis and focal nephritis and concluded that acute focal nephritis is not a clinical entity It must be admitted that clinical differentiation is difficult in some cases and impossible in others However the fact remains that in patients with almost any infection hematuria proteinuria and cylindruria may occur and necropsy reveal only the focal lesions described in this chapter with none of the diffuse changes of glomerulonephritis Clinically the differentiation is important For example when red blood cells are found in the urine in such conditions as viral pneumonia or typhoid fever the clinician knows that the urinary findings bespeak what is here termed focal nephritis which will hardly influence the course of the primary disease and the chances are exceedingly small that they herald the onset of glomerulonephritis with its uncertain outlook Theoretically also the distinction between focal nephritis and diffuse glomerulonephritis is important It was seen in Chapter 19 that glomerulonephritis is *not* due to the invasion of the kidneys by microorganisms but that allergic factors are concerned in its causation On the other hand there is good support for the view that focal nephritis results from the direct action of bacteria which have reached the kidney and is really more closely related to hematogenous abscess of the kidney than to glomerulonephritis

Focal nephritis is far less frequent than in presulfonamide and antibiotic days *Pari passu* with the control of typhoid fever hemolytic streptococcus infection and various other bacteremias which were formerly causes of focal nephritis the incidence of the latter has fallen

Etiology and Nature of Focal Nephritis — Apart from the rare cases due to chemical poisoning focal nephritis is a manifestation of infection Moreover it *occurs at the height of the infection* Herein lies as Volhard[8] pointed out an important difference between focal nephritis and acute glomerulonephritis for the latter most often though not invariably occurs after the primary infection has started to subside as is seen in glomerulonephritis complicating scarlet fever and often tonsillitis The close linkage of focal nephritis to the height of the infection is well illustrated by the old observation of Kannenberg[9] that in focal nephritis complicating relapsing fever the renal process waxes and wanes with the periods of the disease

The fact that focal nephritis occurs during the active stage of the primary infection and usually subsides promptly with the latter immediately indicates that this lesion in contradistinction to glomerulonephritis may be due to the direct action of microorganisms on the renal structures The correctness of this view is substantiated by two other lines of evidence

Chapter

23

FOCAL NEPHRITIS, ACUTE INTERSTITIAL NEPHRITIS, AND FOCAL GLOMERULAR LESIONS IN SUBACUTE BACTERIAL ENDOCARDITIS*

FOCAL NEPHRITIS

During the course of various infections there may appear in the urine—which was previously normal or presented only the characteristics of febrile proteinuria—blood, larger amounts of protein and numerous casts. Edema and hypertension are absent, and impairment of renal function is very rarely significant. Indeed there is almost always little or no evidence of a renal lesion apart from the urinary findings, and the course of the primary disease is generally not notably influenced. Anatomically there are *focal* inflammatory and regressive lesions in the glomeruli, tubules and interstitium.

In the past, such cases have generally not been clearly differentiated from acute glomerulonephritis—both being grouped with the focal glomerular lesions of subacute bacterial endocarditis under the collective term of acute hemorrhagic nephritis—though they differ distinctly from the latter pathogenetically, anatomically and, as a rule, clinically. Focal non-embolic nephritis was first adequately differentiated by Scheidemandel[1] and Volhard and Fahr.[2] The latter expressed their conception of the nature of the process in the term *focal glomerulonephritis*. During World War I Munk[3] made an exhaustive study of the occurrence of this variety of renal disease and spoke of it as Infektnephritis. In this country Baehr[4] published a study of 14 cases of the disease here under consideration. Christian[5] and his coworkers, O'Hare and Walker,[6] devoted attention to the hemorrhagic nephritides, but it does not seem to me that they differentiated sharply between glomerulonephritis and the renal lesions that form the subject of this section.

The term focal glomerulonephritis has been generally applied to this type of renal disease but is open to the objection that the lesions differ

* The renal lesions discussed in this chapter—focal nephritis, acute interstitial nephritis and the focal glomerular lesions of subacute bacterial endocarditis—all occur as a result of and in the presence of active bacterial infection. For this reason their incidence has decreased enormously since the introduction of antibiotics and many of the manifestations described are of little more than historical interest where antibiotics are in general use.

Erysipelas is rather rarely complicated by acute nephritis—8 times in Jochmann's[14] 463 cases. The large majority of nephritides complicating erysipelas are focal; true glomerulonephritis is exceedingly rare.

Puerperal and other streptococcal infections may also be accompanied by focal nephritis which generally quickly clears up if the primary focus is removed.

PNEUMONIA.—Renal function is unimpaired in the vast majority of patients with pneumonia (MacIntosh and Rennau[12]). Correspondingly it was mentioned above that all varieties of acute nephritis are rare in pneumonia. Most of the few cases observed are focal nephritides and of little consequence as far as the outlook for the patient is concerned, though they tend to occur in very severe cases. The hematuria diminishes rapidly with the drop in temperature or before. The rare instances of glomerulonephritis complicating pneumonia were mentioned above (page 534).

TYPHOID FEVER.—Febrile proteinuria was present in 66 per cent and casts in 37.8 per cent of Osler's 1500 cases; they are of little significance. Curschmann[15] found acute nephritis in 1 per cent and Jochmann[16] in 3.5 per cent of their cases of typhoid fever. It is probable that almost all these cases were instances of focal nephritis; in fact, so experienced a pathologist as Fahr[16] states that he has never seen glomerulonephritis attributable to typhoid bacilli. In the extremely rare instances, as those described by Howland,[17] in which glomerulonephritis does complicate typhoid fever, it is probably either a reactivation of chronic glomerulonephritis which occurred in a case observed by Munk, or the result of secondary infection.

Anatomically, focal nephritis is found. These cases were long ago studied by Wagner,[18] who differentiated two groups. In the first, focal hemorrhagic glomerular lesions predominate, while in the second interstitial infiltration is the most prominent feature. The interstitial infiltration may go on to softening and the formation of miliary abscesses; these were present in 7 of Osler's 137 fatal cases of typhoid fever. Munk also describes a third group in which there is extensive necrosis of the tubular epithelium. Typhoid bacilli may be found in the lesions and in the lumen of the tubules.

OTHER INFECTIONS.—Focal nephritis occurs on very rare occasions in various other infectious diseases—scarlet fever, measles, cerebrospinal fever, influenza, rheumatic fever and many others. In all it is transitory and of little significance.

It should be mentioned, however, that according to the literature focal nephritis occurs with much greater frequency in malaria and relapsing fever; with the first of these diseases the writer has had little personal experience and with the second none.

Malaria.—Thayer[19] found 26 instances of acute nephritis in 1032 cases of malarial fever. Seven of these occurred in tertian fever, 1 in quartan, 6 in æstivo-autumnal and 1 in an uncertain type. On the other hand, Giglioli,[20] in his extensive studies in British Guiana, found that renal disease did not complicate æstivo autumnal fever but occurred in 4.23 per cent of his patients with tertian malaria and 48.57 per cent of those with quartan fever. Contrary to these investigators, Munk[21] did not observe

1 At necropsy the causative organism (streptococcus, pneumococcus, typhoid bacillus, malaria plasmodium, etc.) can frequently be demonstrated in the renal lesions. This has recently been denied by Allen[10] but many years ago, when these lesions were carefully studied at Mount Sinai Hospital, organisms were repeatedly demonstrated in focal nephritis complicating streptococcic and other infections.

2 Cultures of the urine taken with appropriate precautions often reveal the presence of the causative organism, which is also in contrast to the vast majority of cases of acute glomerulonephritis. Thus streptococci have been found many times in the urine of patients with focal nephritis complicating tonsillitis (Scheidemandel[1] and others) and may even be so numerous as to be seen readily in the stained sediment. The presence of typhoid bacilli in the urine in focal nephritis complicating typhoid fever is, of course, not of great significance.

The evidence is thus very strong that focal nephritis results from the presence in the kidneys of microorganisms which have been brought there by the blood stream from a distant focus. In fact, in a case in Mount Sinai Hospital of focal nephritis complicating tonsillitis, streptococci were cultivated from the blood. Focal nephritis is then more closely related to the focal glomerular lesions of subacute bacterial endocarditis and to multiple hematogenous abscesses of the kidneys than to glomerulonephritis which is of toxic origin. On histological examination of kidneys containing hematogenous abscesses it is not uncommon to find widely distributed focal nephritis.

It has been suggested that the lesions of focal nephritis are caused by bacteria in the process of excretion into the urine ("Ausscheidungsnephritis" of the Germans). Such a conception would account for the fact that when focal nephritis complicates, for example, tonsillitis, there is no clinical evidence that the bacteria disseminated from the tonsils by the blood stream have produced lesions in organs other than the kidney. But it is to be remembered in this connection that discrete inflammatory and necrotic foci akin to those in the kidneys are common in different organs (*e.g.*, the bone-marrow and the liver) in the course of various bacteremias, and generally give no clinical evidence of their presence. In the kidney, however, the examination of the urine reveals the lesions. So it may be, and in some instances this is undoubtedly true, that focal nephritis is but one manifestation of a widespread process.

The incidence of focal nephritis in various infections is considered in the following.

Streptococcal Infections. – Tonsillitis and other varieties of angina were formerly a common cause of focal nephritis, though since the introduction of antibiotics the complication is rarely seen. The hematuria appears at the height of the process in the throat and generally quickly subsides. But it is in the cases that complicate sore throat that the obstinate persistence of microscopic hematuria over long periods of time is most often encountered. The reason, quite probably, is that the infectious focus in the throat, though giving no marked local symptoms, continues to send bacteria into the blood stream.

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any instance of renal disease in several thousand cases of malaria studied in Europe during World War I. Evidently, there are variations in the incidence of renal disease in different groups of cases of malarial fever, the nature of the treatment may also play a part. It should be borne in mind that edema in malaria may be due to hypoalbuminemia not produced by renal disease, Kopp and Solomon[22] found such to be the case in therapeutic malaria.

Anatomical studies have been made by Kiener and Kelsch,[3] Barker,[4] Ewing,[5] and by Italian observers. While in some of the cases true glomerulonephritis is present, in most the description seems to be that of focal nephritis which is often very widespread. In an interesting case studied by Ewing there were extreme degenerative changes and extensive hemorrhages which resulted from the enormous accumulation of parasites in the renal capillaries. Pigmentation of the glomeruli is often found whether or not nephritis is present. Some of the cases become chronic, and Thayer is of the opinion that in lands infested with malaria it may play a not unessential part in the etiology of chronic renal disease. It would seem that a study of the pathological anatomy of these chronic malarial nephritides in regions where such material can be obtained would probably be of great interest for it might yield information as to what changes are produced by a chronic recurrent, focal nephritis, a condition about which nothing is known.

Clinically, the cases of focal nephritis exhibit little more than the presence of blood, protein and casts in the urine. It seems that exceptionally the focal lesions are sufficiently widespread to produce uremia. However, the symptoms of focal nephritis and glomerulonephritis are not differentiated in the older literature.

Relapsing Fever.—Kannenberg[9] found acute nephritis in 8 of 39 cases of relapsing fever. Ponfick[6] and Puschkareff[27] observed renal lesions almost constantly in patients who died in epidemics of relapsing fever. While some of the cases may have been glomerulonephritis as indicated by the presence of edema, the majority seem to have been focal nephritis. In an investigation in Poland during World War I, Munk[3] found the renal lesions in relapsing fever to be focal nephritis.

CHEMICAL POISONING.—Chemical poisoning not uncommonly produces focal nephritis. Arsenic, cantharides and various other nephrotoxic substances may cause focal lesions in the kidney clinically manifested chiefly by hematuria and clearing up rapidly after the noxious substance has been withdrawn.

Pathological Anatomy.—There is nothing characteristic in the gross appearance of the kidney in focal nephritis, the type of lesion present is as a rule first ascertained with the microscope. The kidney may be normal in size or somewhat enlarged, rather soft, and the capsule strips readily. The surface generally appears rather congested and in very severe cases is chocolate colored. The most striking feature is usually the presence of small hemorrhages, which may be few in number or very numerous. The surface of the section is moist, the architecture little altered and the glomeruli stand out as dark or bright red points.

Microscopically, it is seen that most of the glomeruli are normal, apart from frequent congestion. In some however there are lesions. The most prominent of these is usually hemorrhage into the capsular spaces of varying numbers of the glomeruli. The walls of individual capillaries are swollen but the vast majority are free from such change. In some of the tufts there are found small foci of endothelial proliferation, slight accumulation of leucocytes and swelling of the capillary walls but these rarely involve more than a part of the glomerular tuft and are seldom widespread. Here and there slight proliferation of Bowman's capsule or capsular adhesions may be seen, particularly over an area of nuclear proliferation within the tuft. In some of the capsular spaces which do not contain blood, there

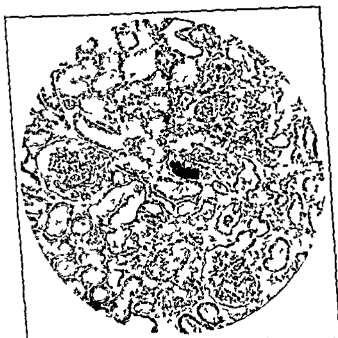


Fig 36 —Focal nephritis. Hemorrhage into capsular spaces and tubules and foci of tubular destruction with cellular infiltration

may be coagulated exudate. But it is to be emphasized that many and in fact most often considerably the greater part of the glomeruli are unaltered.

The epithelium of the tubules in most cases shows cloudy swelling. In severe processes there may be focal necroses of the tubular epithelium in which the nuclei do not take the stain. Necrosis was very extensive in some exceedingly severe cases of typhoid fever studied by Munk. There are usually foci of fatty change and desquamation of the tubular epithelium but these are not extensive. Some of the tubules contain blood and others granular debris or well formed casts but the latter are generally not abundant. In some cases of focal nephritis complicating typhoid fever Munk found that the cells of the primary convoluted tubules gave a strong iron reaction, evidently from resorption of blood pigment from the lumen

As a rule, scattered interstitial infiltrates largely of lymphocytes, are present they may be around the glomeruli Small interstitial hemorrhages are present in many instances The vessels are unaltered apart from the usually well marked congestion of the intertubular capillaries

Bacteria (streptococci pneumococci typhoid bacilli etc) can often be demonstrated in the lesions and sometimes in the lumen of the tubules

Symptomatology —In the vast majority of instances focal nephritis is merely an incident in the course of an infectious disease not influencing the course of the primary malady and discovered only as a result of the urinary abnormalities

Hematuria is the cardinal symptom It usually appears at the height of the infectious process (tonsillitis erysipelas scarlet fever typhoid fever etc) Most of the cases exhibit only microscopic hematuria since the introduction of antibiotics hematuria visible to the naked eye has become very rare The duration of the hematuria is variable it generally diminishes after a few days but isolated red cells may be found in the sediment for long periods Improvement in the primary disease is most often quickly followed by diminution in the hematuria if it has not previously cleared up When the fever is quickly terminated by an antibiotic, the red cells in the urine usually disappear very soon

Accompanying the blood in the urine are protein generally but moderate in quantity and varying numbers of hyaline granular and blood casts Leucocytes are often abundant and there may be epithelial cells It is not uncommon to find bacteria in the stained sediment particularly in cases complicating tonsillitis

Renal function is unimpaired in the vast majority of instances However Volhard mentions a case with transitory impairment of renal function in such instances the foci must be extremely numerous As a rule the urinary volume is diminished presumably as a result of the fever

The absence of edema and hypertension is a basic criterion for the diagnosis Hypertensive retinopathy is of course likewise absent

Occasionally there is pain in the lumbar region as a rule transitory and not severe

The unusual complication of *typhoid fever* by focal nephritis warrants some further discussion though now of little more than historical interest in this country Focal nephritis generally occurs in severe cases of typhoid fever Almost always it causes no symptoms apart from the urinary abnormalities and does not in itself influence the outlook The onset of the hematuria is most often during the fastigium and it clears up rapidly with defervescence There is neither hypertension nor edema and it may be questioned whether the so-called uremia which is described in the older works was actually such or a manifestation of typhoid toxemia The mortality is relatively high in typhoid fever complicated by focal nephritis apparently because this complication occurs mostly in previously severe cases Jochmann[15] observed 50 per cent mortality in such patients but other clinicians have not noted so high a rate

There are extremely rare instances in which the manifestations of severe focal nephritis mark the onset of typhoid fever the *Nephrotyphus* or *fievre typhoide a forme renale* of Continental authors I have seen one such

case in which the patient was admitted to Mount Sinai Hospital with the diagnosis of acute nephritis because of the marked hematuria and was revealed only after several days to be suffering from typhoid fever. The patient recovered, though the prognosis in "Nephrotyphus" is generally rated to be very bad.

Diagnosis.—The diagnosis of focal nephritis rests on the appearance during the course of an acute infectious disease of hematuria, proteinuria and cylindruria in the *absence of edema and hypertension*. Impairment of renal function is extremely rare in focal nephritis. Of course there are many cases of glomerulonephritis which present this picture, and to establish the diagnosis considerable observation may be necessary. There are cases that clear up in which one is never sure if focal nephritis or glomerulonephritis was present. It should be remembered that glomerulonephritis is extremely rare as a complication of *other than* streptococcal infections. The differentiation between acute glomerulonephritis and focal nephritis is further discussed on page 582.

Prognosis.—The prognosis is excellent; the renal lesions usually clear up promptly with recovery from the *primary* infection or even before it. Nor does focal nephritis exert a notably unfavorable effect on the prognosis of the initial disease, though the renal complication is more likely to occur in severe cases.

In unusual instances of focal nephritis complicating tonsillitis, slight hematuria, usually only microscopic, may persist for long periods, even over a year. The patients feel well otherwise. Such cases offer great difficulty in deciding whether or not glomerulonephritis is present. Ultimately, however, they clear up, sometimes only after tonsillectomy. There may be recurrences of focal nephritis with succeeding attacks of tonsillitis.

Treatment.—The treatment is that of the primary infection, the renal condition requiring no special therapeutic measures. In the cases complicating tonsillitis, it is well not to remove the tonsils during the acute stage of the renal process, for the operation is often followed by increase in hematuria and, according to Scheidemandel,[1] of the number of bacteria in the urine. After the blood has disappeared from the urine, diseased tonsils should be removed. If slight hematuria is very persistent, tonsillectomy should be carried out, though it is possible that the amount of blood in the urine will increase for several days, but this soon disappears. Baehr[4] observed a case of focal nephritis which was cured by repeated washings of the infected antrum of Highmore.

ACUTE INTERSTITIAL NEPHRITIS

We have seen that there is no adequate justification for the use of the term chronic interstitial nephritis as commonly applied to those renal diseases which are characterized clinically by arterial hypertension and its consequences in the absence of edema, and anatomically by extensive fibrosis of the kidneys. There is, however, an acute interstitial nephritis, though it can rarely, if ever, be recognized *intra vitam*. Councilman[29] defines the condition as follows: "An acute inflammation of the kidney characterized by cellular and fluid exudation in the interstitial tissue

accompanied by, but not dependent on, degeneration of the epithelium, the exudation is not purulent in character, and the lesions may be both diffuse and focal." According to Councilman the first case of acute interstitial nephritis was published by Biermer[30] in 1860, though Biermer's description does not seem unequivocal to me. The renal lesion was later described by Wagner[18] under the name of acute lymphomatous nephritis, however under this term he also included some cases of the variety here known as focal nephritis. The best anatomical study is that of Councilman.

As would be anticipated from the importance of septic infection in its etiology, acute interstitial nephritis has diminished greatly in frequency since the introduction of antibiotics. I have not seen a case in several years.

Etiology.—Acute interstitial nephritis complicates septic states, notably secondary streptococcal invasions in the acute specific infectious diseases of childhood. Thus Councilman found acute interstitial nephritis at necropsy in 24 of 100 cases of diphtheria, 5 of 20 of scarlet fever, 5 of 23 with both diphtheria and scarlet fever, and 2 of 5 with both diphtheria and measles. An even higher incidence was found by Kannerstein[31] in scarlet fever, diphtheria and measles, as well as in influenzal meningitis. It should be borne in mind that these figures refer to fatal cases which are generally complicated by secondary infections with bacteremia, and that the incidence of acute interstitial nephritis in non-fatal cases is undoubtedly far smaller. Acute interstitial nephritis also occurs in rare cases of sepsis following sore throat, erysipelas, typhoid fever, smallpox, infected wounds, etc. In addition to its occurrence in septic states, Kimmelstiel[32] observed extensive interstitial cellular infiltration in hemolytic reactions, especially following blood transfusion, and in the hepato-renal syndrome. As mentioned above the frequency of acute interstitial nephritis has diminished greatly since the introduction of antibiotics. However Allen[33] found that acute interstitial nephritis may be a manifestation of sulfonamide reactions.

Cultures from the kidney were negative in many of Councilman's cases; in others colon bacilli, streptococci and staphylococci were grown, findings to which he attributes little significance in view of the probability of post-mortem invasion. Not uncommonly streptococci can be demonstrated in sections of the lesions.

Duval and Hibbard[34] have produced acute interstitial nephritis in the dog by inoculation with living cultures of scarlet fever streptococci. This finding contrasts with the glomerular lesions which they produced by the toxic filtrate in the absence of the living organisms (page 557) and indicates that acute interstitial nephritis is due to invasion of the kidneys by the organisms rather than to the action of the toxic products as in glomerulonephritis. On the other hand Kimmelstiel, who observed acute interstitial nephritis in association with hemolytic reactions and acute liver damage, regards it as a hyperergic response to protein products. Allen's observations of acute interstitial nephritis in sulfonamide reactions have similarly led him to regard it as of allergic pathogenesis. That other organs than the kidney are also sometimes involved will be pointed out below.

Pathological Anatomy.—In most instances the macroscopic appearance of the kidney is not characteristic. It is enlarged, often very considerably,

and soft The surface is smooth and may be dotted with hemorrhages of various sizes On section it is seen that the enlargement is due to a thickening of the cortex which may be very marked The surface is moist and the normal markings obscured There are sometimes linear and wedge-shaped hemorrhages in the cortex between which are yellowish areas thus producing a striated appearance which Aschoff[24] considers as very characteristic

Microscopically one is immediately struck by the presence of dense cellular infiltration The cells lie closely packed between the tubules and around the glomeruli The distribution of the infiltrates is irregular in some places they seem diffuse while elsewhere the focal arrangement is very obvious In other cases there may be only isolated nodular infiltrates

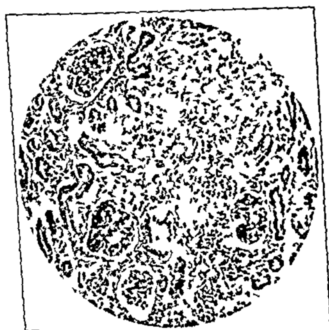


Fig 37 —Acute interstitial nephritis in a child aged eighteen months with sepsis Extensive infiltration of plasma cells and lymphocytes in the interstitium

According to Councilman the lesions are most marked in the boundary zone of the pyramids next under the capsule and thirdly around the glomeruli In many areas the exquisitely interstitial nature of the infiltration is seen the masses of cells separate the individual uninjured tubules from one another and surround the intact glomeruli In other places the cells have broken through the tubules into the lumen injuring, loosening and finally destroying the tubular epithelium so that ultimately masses of infiltrating cells without any discernible renal parenchyma in their midst are to be seen The glomeruli resist much better apparently intact Malpighian bodies may be seen completely surrounded by the infiltrating cells but they too are finally compressed and destroyed Before this capillary thromboses and other changes in the glomeruli are to be

seen There are also hemorrhages, often of linear distribution at the borders of the infiltrates Groups of tubules may contain blood

The nature of the cells composing the infiltrates varies in different cases Councilman points out that in many instances the infiltrating elements are almost all plasma cells Very commonly however, lymphocytes predominate There are few polymorphonuclear leucocytes in the lesions But according to Huebschmann[36] polymorphonuclears may predominate in the first stage Munk[37] observed a case of acute interstitial nephritis complicating hemorrhagic smallpox in which there were numerous eosinophiles in the infiltrates

The rare cases of *acute interstitial edema* of the kidneys are probably closely related to acute interstitial nephritis In a case of this type that I saw some years ago, the clinical picture was that of a febrile infection with fulminant renal insufficiency

Pathogenesis —Councilman and Schridde[38] have shown that the cells composing the infiltrates emigrate from the blood vessels *i e* that the inflammation is predominantly exudative rather than proliferative That the exudative process is not confined to the kidneys is indicated by the investigations of Landsteiner,[39] who has shown in cases of acute interstitial nephritis complicating scarlet fever that histologically similar infiltrates are to be found in the suprarenals, liver meninges and other organs The above-mentioned case described by Munk of acute interstitial nephritis complicating smallpox in which one third of the infiltrating cells were eosinophiles, is very interesting in this connection He found similar infiltrates containing eosinophiles in the liver spleen lymph glands brain pancreas and other organs In view of the presence of infiltrates similar to those in the kidney in other organs, Munk looks upon acute interstitial nephritis not as a pure kidney disease but as a generalized cellular exudation caused by the organism of the primary infection of which the renal lesion is but one manifestation The exudate may be composed of lymphocytes plasma cells, or as in the above mentioned case of smallpox largely of eosinophiles But whatever the variety of cell it is the same in the different organs thereby indicating the unity of the process Further investigations on the various organs of the body in acute interstitial nephritis to confirm these views advocated by Munk would be highly desirable I saw a case in which acute interstitial nephritis was accompanied by plasma cell infiltrates in various organs but in other cases no extrarenal infiltrates were found

Clinical Picture —Acute interstitial nephritis is first recognized with certainty at the postmortem table for the disease produces no characteristic manifestations during life It occurs most often in the course of severe septic infections and even in retrospect it is often impossible to discern any notable influence of the renal lesion on the clinical course There is neither hypertension nor edema Even proteinuria may be slight or absent Occasionally there is hematuria The urinary volume is usually diminished but often not beyond the degree that might be expected in any highly febrile patient Rarely there is complete anuria as in Biermer's original patient, who passed practically no urine for ten days In such unusual cases enormous nitrogen retention may occur (Noble[40]) and death is due to uremia

Because of our inability to recognize acute interstitial nephritis during life it is not known how many patients recover. It would seem that survival must be very rare for so far as is known acute interstitial nephritis occurs most often as a complication of very severe septic infections which usually terminate fatally. However it is possible that this variety of case is the only one recognized because the diagnosis is made only at post mortem. It has been thought that healed cases of acute interstitial nephritis which are not recognized at the time may play a considerable role in the pathogenesis of contracted kidney manifesting itself many years later. Aschoff[39] believes that some instances of contracted kidney may be traced with probability to antecedent acute interstitial nephritis. I know of no evidence that this actually occurs. Loewenthal[40] described a case of what he considered as true chronic interstitial nephritis but considered that it was alone in the literature. Rich[41] published 19 cases of interstitial infiltration of the kidneys in syphilitics and doubtless of luetic origin. But it would seem that this lesion, a true chronic interstitial nephritis, is rarely if ever of great clinical significance. Actual chronic interstitial nephritis, i.e., a chronic inflammatory process of clinical significance originating *between* the nephrons, apparently occurs only in pyelonephritis.

Diagnosis.—As stated above, the certain diagnosis of acute interstitial nephritis is almost impossible during life. If extreme oliguria or anuria sets in during the first week of septic scarlet fever before the period when glomerulonephritis occurs, the existence of acute interstitial nephritis may be suspected.

Prognosis and Treatment.—Since the diagnosis cannot be made with any assurance, the prognosis and treatment are of necessity those of the primary disease. If the renal condition could be recognized or very strongly suspected and the oliguria was extreme, decapsulation would seem logical in view of the swelling of the kidney. But since the antibiotics came into use acute interstitial nephritis seems to have practically disappeared.

FOCAL GLOMERULAR LESIONS IN SUBACUTE BACTERIAL ENDOCARDITIS

Harbitz[43] long ago noted that hemorrhagic nephritis is common in protracted cases of bacterial endocarditis of the type now known as subacute bacterial endocarditis (Libman[44]). That the hematuria in these cases is usually not due to diffuse glomerulonephritis but to focal glomerular lesions produced by minute bacterial emboli from the endocardial vegetation was maintained by Lochlein[45] and strongly supported by extensive material by Baehr.[46] The process has been generally known as embolic non-suppurative focal nephritis (Loehlein). Baehr and Libman speak of them as the embolic glomerular lesions of subacute bacterial endocarditis. In previous editions of this book the lesions in question have been designated as *multiple glomerular embolization*. But inasmuch as the grossly embolic nature of the lesions seems doubtful, the purely descriptive term *focal glomerular lesions* of subacute bacterial endocarditis will be used.

Since the introduction of antibiotics focal glomerular lesions have become much less common findings at necropsy (*cf.* Spain and King).[48]

Etiology.—The focal glomerular lesions to be described below occur almost exclusively in subacute bacterial endocarditis. By careful searching, the lesions are found in a very high proportion of cases. Baehr observed them in 23 of 25 kidneys in subacute bacterial endocarditis due to the Streptococcus viridans. Miller and Branch[47] have also found them in a case due to an influenza-like bacillus. Focal glomerular lesions were present in a case, at Mount Sinai Hospital, of subacute bacterial endocarditis due to the pneumococcus Type II, and probably in another due to the influenza bacillus; in both these cases there was also diffuse glomerulonephritis. Focal glomerular lesions occur not only in the active phases of subacute bacterial endocarditis but also in Libman's healed stage; Baehr found the lesions in 6 of 7 healed cases.

On rare occasions, the characteristic focal lesions in the glomeruli are encountered in conditions other than subacute bacterial endocarditis. Baehr mentions one instance in which the seemingly typical lesions were present in an obscure infection without endocarditis. Bell[48] has also seen the characteristic foci in a case of sepsis from an infected wound and erysipelas but *without* endocarditis. And Fahr[49] describes a case of otogenous sinus thrombosis in which the histological picture of focal glomerular lesions was *produced by proliferation of cocci within the glomerular loops* so as to block them and result in foci of coagulation necrosis. But it is to be emphasized that such examples of morphologically typical focal lesions in the absence of endocarditis are of extreme rarity.

On the basis of the work of Loehlein, Baehr and Libman, focal glomerular lesions have been considered almost pathognomonic of subacute bacterial endocarditis. However, Bell has reported that in 3 of 104 cases of rheumatic endocarditis, capillary thromboses were found which correspond to the early stages of the embolic lesions. The pathogenetic identity of these capillary thromboses in rheumatic fever with the focal glomerular lesions of subacute bacterial endocarditis seems improbable; for if such were the case one would also expect to encounter the fully developed lesions in a disease of such varying duration and with so many recurrences as is rheumatic fever. According to material studied at Mount Sinai Hospital, New York, by Libman, Baehr and Klemperer, the typical embolic lesions are *not* encountered in uncomplicated rheumatic fever. Bell also reports finding focal glomerular lesions in 4 of 56 cases of acute endocarditis (defined as being of less than six weeks' duration) and in 4 of 69 cases of secondary endocarditis (*i.e.*, endocarditis in which a primary infectious focus is demonstrable, not recognized clinically, and presumably a terminal infection). It seems probable that at least some of these cases of "acute" endocarditis would fall within Libman's conception of subacute bacterial endocarditis, in which the *clinical* course may be decidedly less than six weeks if it is terminated by some such accident as a cerebral embolus shortly after the first symptoms. Subacute bacterial endocarditis is characterized more by the nature of the endocardial lesions than by the duration of the disease.

Pathological Anatomy.—The kidneys are normal in size or more often somewhat enlarged. The capsule usually strips readily from the smooth surface. However, in older cases there may be some irregularity of the

surface with adhesions of the capsule due to small indurated scars The most characteristic feature though not invariably found is the presence of small usually irregular hemorrhages often very numerous and imparting to the kidney an appearance aptly described by the term "flea bitten" kidney used by Horder [9] Large and small infarcts are common, resulting from the occlusion of large vessels by emboli from the endocardial vegetations

Microscopically, the characteristic glomerular lesions are found the same kidney generally exhibiting various stages of their development



Fig 38 — Flea bitten kidney of focal glomerular lesions in subacute bacterial endocarditis. The surface is sprinkled with punctate hemorrhages

The proportion of glomeruli containing lesions varies Baehr found from 2 to 75 per cent involved However there are exceptional cases in which practically every glomerulus exhibits lesions Baehr noted that the proportion of affected glomeruli varies in different parts of the same kidney Also the lesions usually involve but a part of a glomerulus and there may be two or more in a single tuft

The process starts with swelling and granular change of the walls of one or more capillary loops situated in any part of the tuft This progresses

until there is a homogeneous mass which stains deeply with eosin in the ordinary hematoxylin-eosin preparation, and contains nuclei in various stages of disintegration. The lesion is thus a typical coagulation necrosis. Very striking is the paucity of the cellular reaction around the lesion though there may be a few leucocytes or slight proliferation of fixed cells adjacent to the necrotic area. But if the involved capillaries are in contact with Bowman's capsule there is usually localized proliferation and desquamation of the epithelial cells of the visceral layer of the capsule directly over the lesion. Well defined epithelial crescents may form. Localized capsular adhesions form over the involved area. Very commonly the injured capillaries rupture into the capsular space and fill it with blood.

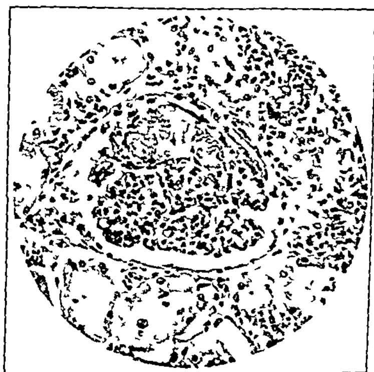


Fig. 39.—Focal glomerular lesion in subacute bacterial endocarditis. Large lesion in a glomerulus. Note the normal appearance of the rest of the glomerulus and the absence of inflammatory reaction about the area of necrosis.

The uninvolved portions of the glomerulus may present no striking change or there may be proliferative glomerulitis of varying degree.

Scarred lesions are usually also to be found and in the healed cases may be the only ones present. Healing of the lesions is marked by connective tissue replacement of the necrotic area. The resultant scar which ultimately becomes hyaline is sharply demarcated from the rest of the glomerulus and merges with the interstitial connective tissue outside of the capsule. Loehlein points out that when an entire glomerulus is thus obliterated, the resulting hyaline area often differs from that in diffuse glomerulonephritis in that the transition to the surrounding tissue is gradual and not sharply defined.

By the application of the azocarmine stain Bell[55] has found that the embolic lesions are of two morphogenetically distinct varieties the hyaline and the fibrous The former stain bright red and the fibrous lesions deep blue with azocarmine Bell finds that the hyaline lesion starts as an intracapillary thrombosis with secondary necrosis of the capillary wall the entire mass ultimately disintegrating and disappearing On the other hand Bell s fibrous lesions originate in thickening of the basement membrane of the group of capillaries so that the lumens are ultimately obliterated without the supervention of thrombosis the thickened basement membrane gives the staining reactions of collagen Bell found both types of lesion present in most cases of subacute bacterial endocarditis but in some instances only one or the other was found

As a rule some of the tubules contain blood Baehr has found in serial sections that these tubules lead to injured glomeruli In cases with few glomerular lesions the tubules likewise show little change But when the glomerular lesions are widespread there may be fairly extensive areas of tubular atrophy The tubules often show well marked fatty change collapse and atrophy of the epithelium Ultimately in cases of sufficiently long standing the atrophic tubules disappear completely and areas of replacement fibrosis take their place There is often considerable lymphocytic and leucocytic infiltration of the newly formed connective tissue The atrophic changes in the tubules which are always patchy and usually not prominent are evidently secondary to the destruction of the appertaining glomerulus That the atrophy is ever prominent enough to lead to a notable degree of contraction of the kidney has not so far as I am aware been demonstrated

On the basis of anatomical observations by Lohlein and Baehr it was long generally accepted that at least some of the glomerular lesions are produced by minute bacterial emboli from the endocardial vegetations With the Gram Weigert stain Baehr found emboli containing streptococci in the glomerular lesions of 5 cases The bacteria were demonstrable only in early cases evidently succumbing rapidly after settling in the kidney Clawson[61] was able to produce glomerular lesions akin to those found in subacute bacterial endocarditis by the intracardiac injection of an agar suspension of the Streptococcus viridans Kinsella and Sherburn[2] also noted glomerular lesions in conjunction with experimental streptococcus endocarditis

Contrariwise many have doubted the embolic nature of the lesions (Longcope[53] Jungmann[54] Allen[55]) Evaluated against the embolic pathogenesis have been the great difficulty of demonstrating bacteria in the lesions and their absence in acute bacterial endocarditis Longcope considered the possibility that the lesions represent focal allergic reactions But to the writer the fact that the lesions occur almost exclusively in subacute bacterial endocarditis with its friable vegetations seems to speak very strongly for the embolic origin The emboli need not necessarily be large enough to plug mechanically a capillary lumen and thus cause ischemic infarction the mere lodging of minute groups of bacteria within the glomerular capillaries can conceivably result in the lesions by producing necrosis of the capillary wall with resultant thrombosis

Clinical Findings.—In the vast majority of cases the only clinical manifestation of the focal glomerular lesions is hematuria. Either the patient or the doctor may notice that the urine is bloody, or far more often the red cells are first revealed by microscopic examination of the sediment. The hematuria varies greatly in most instances, diminishing or even disappearing one day to return again. In other cases it is persistent for months. The quantity of blood thus lost is generally not great; sudden copious hematuria points to gross infarction, being then often accompanied by the characteristic pain. In addition to blood the urine contains casts of various sorts and protein, usually moderate in amount.

The course of subacute bacterial endocarditis is hardly ever modified by the focal glomerular lesions. There is neither hypertension nor edema as a result of this variety of renal lesion. Baehr found also that it does not produce impairment of renal function. An exception is constituted by rare cases in which the focal glomerular lesions are so widespread that renal insufficiency results as manifested by diminution in concentrating power and retention of urinary constituents in the blood. Such cases have been described by Bell, Boyarsky[6] *et al.* and others. How rarely focal glomerular lesions produce renal insufficiency may be appreciated from the fact that in over 800 cases of subacute bacterial endocarditis Dr. Emanuel Libman told me that he had never observed it. Since antibiotics came into use renal insufficiency is not as rare a complication of subacute bacterial endocarditis (*cf.* Villarreal and Sokoloff[9]) but while focal lesions may be present, glomerulonephritis is then almost always present.

Diagnosis.—The occurrence of persistent hematuria, microscopic or macroscopic, in a patient with subacute bacterial endocarditis immediately suggests the presence of focal glomerular lesions; in fact on very rare occasions the existence of subacute bacterial endocarditis is first discovered as a result of the search for the cause of such hematuria. However, hematuria in subacute bacterial endocarditis may also be due to large infarction of the kidney or to diffuse glomerulonephritis. As mentioned above, in such a patient sudden copious hematuria, usually accompanied by pain in the side or back, points to the existence of a large infarct. Christian's[57] findings indicate that large numbers of erythrocytes in the sediment are more apt to be due to glomerulonephritis than to focal glomerular lesions. Diffuse glomerulonephritis is rare in the active stage of the disease but decidedly more common in Libman's bacteria free stage; in fact Libman states that it is fifteen times as frequent in the latter period of the disease. The presence of edema (not due to myocardial failure or to hypoalbuminemia in cachectic patients) or hypertension in subacute bacterial endocarditis indicates the existence of diffuse glomerulonephritis. The same is true, apart from the rare exceptions just mentioned, of impairment of renal function. However, diffuse glomerulonephritis often occurs in subacute bacterial endocarditis in the absence of hypertension, edema and impairment of renal function; in such cases hematuria due to the diffuse lesion cannot be differentiated from that produced by focal glomerular lesions. It should be remembered in this connection that diffuse glomerulonephritis and focal glomerular lesions are often found in the same kidney.

Prognosis and Treatment — The prognosis and treatment are those of subacute bacterial endocarditis not being influenced by the presence of focal glomerular lesions. In particular the presence of focal renal lesions should not interfere with the attempt to give the patient the ample nourishment with high protein content which is necessary. With successful antibiotic treatment the red cells generally soon disappear from the urine. As mentioned above since the introduction of penicillin focal glomerular lesions are hardly found.

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Chapter

24

ESSENTIAL HYPERTENSION I. CONCEPT AND PATHOLOGICAL ANATOMY

HISTORICAL DEVELOPMENT OF THE CONCEPT OF ESSENTIAL HYPERTENSION

For many years the symptom of hypertension was all but universally regarded as invariably a consequence of preexisting renal disease or arteriosclerosis. It is true that there were individual observers who surmised the existence of hypertension not due to disease of the kidneys or sclerosis of the arteries, and Mahomed[1] even spoke of a "prealbuminuric stage of Bright's disease." However, as Allbutt points out, Mahomed believed that hypertension is inevitably followed by definite disease of the kidneys, and his work had little influence on the conceptions of the nature of hypertension entertained at the time.

With the introduction of the sphygmomanometer into clinical medicine by von Basch,[2] recognition of the type of case now termed essential hypertension was inevitable. Indeed, von Basch himself, who made over 100,000 blood pressure estimations, was very well acquainted with our present essential hypertension, which he termed "latent arteriosclerosis." In 1893 he wrote of observations which he had been making for many years: "There are numerous cases in which examination reveals a high tension of the pulse but the other characteristics of outspoken arteriosclerosis are either absent or but minimal." Von Basch viewed the stage of isolated hypertension as a precursor of arteriosclerosis, hence his term *latent arteriosclerosis*.

It was not von Basch, however, but Allbutt in England and Huchard[3] in France who by their keen clinical observations and brilliant writings brought the medical profession to a realization of the enormous frequency of preternaturally high blood pressure in the absence of clinically significant morphological changes in the kidneys and arteries.

Allbutt arrived at a recognition of the occurrence of isolated hypertension through following patients with increased arterial tension over periods of many years. He mentions in particular one woman with high blood pressure whom he watched for eighteen years, but "years passed on and the dreaded Bright's disease never appeared" until she finally died of cerebral hemorrhage. Allbutt named such cases hyperpiesia after the predominant symptom and brought order into the previously confused hypertension-kidney disease-arteriosclerosis group by differentiating:

1. Hyperpiesia, in which high blood pressure dominates the clinical picture with little renal involvement.

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46 BAEHR J Exp Med *15* 330 1912 Am J M Sci *144* 327 1912 Arch Int Med *27* 262, 1921
47 MILLER and BRANCH Arch Int Med *32* 911 1923
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were termed pseudoleukemia until some of the individual diseases thus characterized (Hodgkin's disease, lymphosarcoma, leukopenic leukemia, reticulum-cell sarcoma, etc.) were differentiated. Similarly, it is to be hoped the *true nature* of the individual diseases now grouped as essential hypertension will be revealed and this term will go the way of pseudoleukemia. Indeed a small beginning in this direction has already been made. Not many years ago the cases of essential hypertension due to tumors of the suprarenal cortex or medulla, to basophilic adenoma, or to *obstruction* of the stem of the renal artery (page 677) would have passed as essential hypertension without further qualification. Unfortunately these conditions are infinitesimal in frequency compared *to the totality* of cases of essential hypertension.

PATHOLOGICAL ANATOMY OF ESSENTIAL HYPERTENSION

At the necropsy of an individual who suffered from essential hypertension cardiac hypertrophy is all but invariably found. Less constant but still present in the large majority of instances is arteriolosclerosis of a degree far more pronounced than occurs in normotensives of the same age. The third common anatomical finding in essential hypertension consists in alterations in the kidneys correlated with and apparently secondary to the changes in the small arteries. Most patients with essential hypertension also have a high degree of atherosclerosis of the large arteries, but this is of course also common with normal blood pressure. Finally, in those patients in whom the blood pressure has risen to exorbitant heights with *the* clinical picture of malignant hypertension, arteriolar necrosis may be found. The lesions just enumerated are common to all etiologic varieties of hypertension, being conditioned principally by the duration and severity of the hypertension and the age of the patient. It is in the absence of the specific renal lesions of glomerulonephritis, pyelonephritis, *glomerulosclerosis*, etc., that the anatomical findings of essential hypertension differ from those of other forms of high blood pressure.

The Kidney in Essential Hypertension.—In a large majority of cases of essential hypertension the kidneys are found at necropsy to be *more or less damaged*. The renal lesions of essential hypertension were formerly not differentiated from those of chronic glomerulonephritis, both being united in the concept of "chronic interstitial nephritis." However, later investigations showed conclusively that in essential hypertension the changes in the kidneys are secondary to disease of the small arteries—the so-called arteriolosclerosis—and in recent years the term *arteriolosclerotic kidney* has been appropriately applied to the renal lesions found in the vast majority *of cases* of essential hypertension.

It is important that the *arteriolosclerotic kidney* be sharply differentiated from the *arteriosclerotic kidney* as originally described by Ziegler.[18] In the arteriosclerotic kidney the renal lesions are the result of arteriosclerosis of the large renal vessels, usually a part of generalized arteriosclerosis in old individuals. The arteriosclerosis of the large vessels results, through infarction, in the production of isolated large scars in the kidneys, irregularly distributed and usually not very numerous. Between these large scars

2 Bright's disease, the true renal disease with or without high blood pressure

3 Decrescent arteriosclerosis the senile atheroma of the large arteries not necessarily associated with high blood pressure

Almost simultaneously with Allbutt, Huchard recognized the frequency of non nephritic hypertension He wrote 'Arterial hypertension is the *cause* of arteriosclerosis, it precedes by a longer or shorter time the evolution of the various diseases (arterial cardiopathies and nephritides) which are themselves dependent on the vascular sclerosis' To emphasize the fact that the hypertension antedates the sclerotic changes in the vessels and kidney he termed the condition 'presclerosis

In this country the disease—doubtless more accurately diseases—was first extensively studied by Janeway [5] and next by Moschcowitz [6] Christian [7] O'Hare [8] Keith Wagener and Kernohan [9] Bell and Clawson [10] and many others

At present this disease—the prealbuminuric stage of chronic Bright's disease of Mahomed the latent arteriosclerosis of von Basch, the hyperpiesia of Allbutt the presclerosis of Huchard the hypertensive cardiovascular disease of Janeway the benign and malignant sclerosis of Volhard and Fahr[11]—is most widely known in this country as *essential hypertension* a term introduced by Frank[1] (*essentielle Hypertonie* really essential hypertonia)

The concept of essential hypertension includes those patients with high blood pressure in whom none of the known causes (listed on page 272) of clinical hypertension is demonstrably operative * *The concept is thus a negative one* and the definition is very seriously defective in that it defines solely by exclusion but in our present ignorance of the actual etiology it does not seem feasible to define essential hypertension in any more satisfactory way *The very term essential hypertension is a confession of ignorance—and this is its chief virtue* The noun expresses the dominant clinical manifestation and the adjective serves the double function of forewarning of our ignorance of the cause of the hypertension and differentiating it from nephritic hypertension All that the term essential hypertension really means is hypertension of unelucidated origin But it is a very necessary term for the hypertensions of unknown origin are far more frequent than those due to nephritis suprarenal tumor or other known causation The concept of essential hypertension is merely a stop gap necessitated by our present ignorance It seems highly probable in fact almost certain that essential hypertension is merely a collective concept (a *Sammelbegriff* as the Germans would say) for a number of conditions having in common the positive characteristic of arterial hypertension and the negative one of the absence of known causation The situation is analogous to that which formerly obtained in the group of diseases characterized by generalized enlargement of the lymph glands in the absence of a leukemic blood picture These

* The reader will note that this conception of essential hypertension does not deny the kidney a role even the primary role in the mechanism of elevation of blood pressure All that is said is that what the clinician knows as essential hypertension is not due to inflammation of the kidneys, obstruction along the urinary tract pheochromocytoma or other known cause

arteriosclerotic or other narrowing of the main trunk or first branches of the renal arteries in the cases of essential hypertension without renal arteriolar sclerosis. Moritz and Oldt[18] have reported 4 such cases (see also page 669). However, such cases are extremely rare; the only unequivocal instance that has come under my observation is one in which hypertension set in acutely and operation revealed thrombotic occlusion of a sclerotic renal artery.

Older knowledge of the morphology of the renal vessels in hypertension was derived from post mortem studies. New light has been thrown on the subject by the *intra vitam* observations of Castleman and Smithwick.[8] During sympathectomy on hypertensive patients they removed a segment of the renal cortex 6×3×4 mm in size and containing about 50 cross sections of arterioles and small arteries. In 500 cases they found that these small vessels revealed no pathological changes in 4 per cent, mild alterations in 41 per cent, and severe alterations in the remaining 55 per cent. By severe lesions Smithwick and Castleman understand changes that appear sufficient sensibly to compromise the renal circulation. Their findings are of the utmost importance, for they show that essential hypertension is not the result of structural alterations in the small renal arteries demonstrable by present histologic technique. While Goldblatt[1] has questioned whether the biopsy specimens are large enough to give an accurate index of the state of the renal arteries in general, such does seem to be the case. Castleman and Smithwick found substantial agreement in the findings in both kidneys when they performed bilateral biopsies.

Changes in the renal vessels and kidneys may be practically absent when hypertension results from suprarenal tumor or basophilic adenoma. In the case of suprarenal tumor with great hypertension (heart weight 880 grams) reported by Oppenheimer and the author[22] the renal changes were minimal, and the same has been true in other similar cases in the literature.

THE ARTERIOLOSCLEROTIC KIDNEY.—As was mentioned above, such cases of essential hypertension without renal lesions discoverable at necropsy are decidedly exceptional. Much more commonly one encounters kidneys in which microscopic examination reveals well marked arteriolosclerosis and foci of atrophy of the parenchyma, despite the fact that macroscopically there is no evidence of disease. The surface is smooth and there is no contraction; the consistency is often somewhat increased, or even this may be normal. Not uncommonly, in fact, such kidneys are slightly enlarged as a result of chronic passive congestion, for cardiac failure is the most common cause of death in essential hypertension. Such instances, in which the kidneys appear normal to the naked eye but reveal definite arteriolosclerotic lesions on microscopic examination, are particularly common in relatively young individuals who have succumbed to cerebral hemorrhage, often without knowing that they had hypertension. It cannot be too strongly emphasized that the kidneys should not be pronounced uninjured purely on the basis of the naked eye findings without the confirmation of microscopic examination.

But in a large majority of instances of essential hypertension the evidence of renal damage is immediately evident at the necropsy; the arteriolosclerotic kidney is found. It presents the following characteristics. Usu

the kidney surface is smooth and microscopic examination reveals large areas of intact parenchyma. Sometimes, however, the scars are greater in number and by their intersection produce a coarse pseudogranulation. In such instances, the kidney may be considerably contracted. There may be large, flat, sunken areas corresponding to the closure of particularly large branches. The picture differs notably from the more finely granular appearance of the well-developed arteriolosclerotic kidney.

The arteriosclerotic kidney is usually of little clinical significance. Apart from the rare instances mentioned on page 677, it is not accompanied by hypertension, and while it may cause slight proteinuria, disturbances of renal function are rarely if ever serious. It is the most common anatomical substratum of the so-called senile kidney. Of course, arteriosclerotic and arteriolosclerotic changes are not uncommonly associated in the same kidney.

Essential hypertension is a disease which usually lasts for many years or even three or four decades before death occurs, either as a result of the disease or some independent malady. During this period the renal damage progresses at a varying rate, so it is not surprising that the state of the kidneys as encountered at necropsy varies within wide limits. In some instances the renal damage is minimal, but there are also all gradations down to extremely contracted kidneys as small as those encountered in chronic glomerulonephritis of many years' duration.

Essential Hypertension with Intact Kidneys.—It is decidedly unusual for a case of essential hypertension to come to necropsy without well marked renal arteriolosclerosis being found. As mentioned above, I did not encounter such an instance in 72 cases of essential hypertension which I studied anatomically. However, the study was at Montefiore Hospital for Chronic Diseases and all of the cases had had very protracted clinical illnesses. Since then I have seen several necropsies in which marked hypertension had been present and yet the state of the renal arterioles and small arteries was not abnormal for the age. In one of them the blood pressure had been continuously over 200 mm. systolic and 100 mm. diastolic for at least three years and probably for a considerable time longer.

Cases of essential hypertension in which the kidneys were found normal at necropsy were long ago reported by Pal,[14] von Monakow,[15] Kauffmann[16] and others. Bell and Clawson, in fact, found no arteriolosclerosis in 10 per cent of their cases of essential hypertension, but they consider as arteriolosclerosis only lesions of the vasa afferentia, not including changes in the interlobular vessels. Wallgren[17] had 8 cases of essential hypertension in which the renal arterioles showed no changes other than those corresponding to the age of the individuals. In one of Kauffmann's cases with normal kidneys and no arteriolosclerosis, the patient was known to have had hypertension for twelve years. In his most recent studies Bell[18] finds that at necropsy 17.5 per cent of patients with essential hypertension but no renal insufficiency have renal arterioles and prearterioles which he regards as normal.

The foregoing data refer to the minute intrarenal arterial vessels.

In the light of the experimental production of hypertension by constriction of the renal artery, the question comes up whether or not there was

areas Sometimes the granules have a yellowish tone so that the kidney as a whole appears paler resembling a secondary contracted kidney Small cysts are often present

The kidney substance is tough and hard It offers a considerable resistance to the knife On section it is seen that the cortex is greatly thinned the medullary pyramids less so and the borders between cortex and medulla are often not clearly defined The cortical markings are obscured and irregular scarred areas may be seen descending from the indentations of the surface into the relatively intact parenchyma In the early stages little atrophic areas near the surface may be the only abnormality noted The arteries are rigid have thickened walls and gape

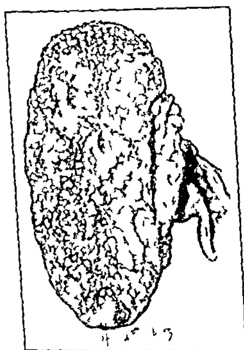


Fig 41 — Late stage of the arteriolosclerotic kidney of essential hypertension (primary contracted kidney) Striking granulation and marked contraction

HISTOLOGY OF THE ARTERIOLOSCLEROTIC KIDNEY —Microscopically the picture varies with the stage of the process In cases which have died at an early phase (for example of cerebral hemorrhage) there may be only arteriolosclerosis while the renal parenchyma is intact or there are a few hyaline glomeruli The next stage is represented by the formation of small foci of atrophy of the parenchyma separated by large areas of intact kidney substance These atrophic foci are most commonly situated at the surface of the organ corresponding to indentations of the surface Often apparently as a result of the arrangement of the blood supply they are wedge-shaped the base of the wedge being at the surface In these areas

ally the capsule is adherent, often so firmly that there is considerable laceration of the kidney substance as the capsule is stripped. In other instances, the capsule comes off readily despite the presence of contraction and granulation. If the kidney is contracted there is an increase in the fatty capsule and the adipose tissue in the hilus. The size of the kidneys varies greatly; they may be somewhat enlarged through congestion or of normal size, but more often there is contraction of varying degree. Rather rarely, extremely small kidneys rivalling the secondary contracted kidney of glomerulonephritis are encountered. As a rule, however, the amount of contraction is less than in the secondary contracted kidney.

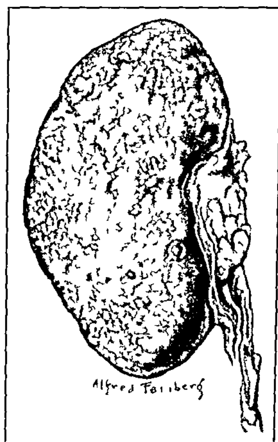


Fig. 40.—The arteriolosclerotic kidney of essential hypertension. Granulation and moderate contraction; two cysts.

The surface is granular. The granules are usually both fine and coarse and often irregularly distributed. Sometimes there is a uniform fine granulation. In other instances there is considerable contraction with little granulation, the surface being but slightly irregular. The granules correspond to areas of relatively intact or even hypertrophic parenchyma, the intervening indentations to atrophic and scarred areas. There may also be large scars due to arteriosclerosis of the large vessels. The general color of the surface is usually a brownish or grayish red (red granular kidney), the granules being mostly lighter in color than the intervening

an early feature of the glomerular process is a thickening and wrinkling of the basement membrane of the glomerular capillaries which is accompanied by a decrease in size of the glomerulus and a simplification of its structure As the arteriolosclerosis progresses and further narrows the lumen of the interlobular or afferent arteriole collapse and hyalinization of the capillaries of the appertaining glomerulus occur All the capillaries of a glomerulus may be simultaneously involved or only some become hyalinized while the rest still contain blood At the border of hyaline areas within a glomerulus there may be slight nuclear proliferation but generalized increase in the nuclear content of the glomeruli and other inflammatory reactions such as occur in glomerulonephritis and less diffusely in the malignant phase of essential hypertension are either absent or are found in but a very small percentage of the glomeruli (Klemperer and Otani— McGregor) Finally the individual hyaline areas fuse The end result is the transformation of the glomerulus into a hyaline sphere staining pink with eosin and containing few or no nuclei

Sometimes the hyalinization of the glomerulus occurs without notable change in the capsule In other instances however there is notable thickening of the parietal layer of the capsule by swelling of the basement membrane (Hersheimer[8]) or more strikingly by the formation of concentric layers of connective tissue around the parietal layer This may occur despite the fact that the tuft of the Malpighian corpuscle is little altered so that the latter is seemingly obliterated by the compression of the thickened capsule In other glomeruli hyalinization of the tuft and thickening of the capsule proceed apace and at one stage the hyaline sphere of the tuft is readily distinguished from the concentrically thickened capsule The hyaline glomeruli finally become completely fibrosed and indistinguishable from the surrounding connective tissue Occasionally calcification of such an obliterated glomerulus occurs If the destruction of glomeruli is very widespread the intact Malpighian bodies may be hypertrophic

The Tubules —The tubule belonging to an obliterated glomerulus atrophies The epithelium becomes smaller and shows fatty and other regressive changes Finally there remains only a cord of cells in the midst of the replacing connective tissue until this also disappears Here as in glomerulonephritis at least two factors are probably concerned in the secondary tubular atrophy (1) The blood supply to the tubules comes almost exclusively from the glomerulus (Cross [7] Langley [illegible]) and is cut down by obliteration of the latter * (2) The cessation of glomerular filtration probably entails a disuse atrophy of the tubular epithelium which no longer has fluid from the glomerulus to resorb In his microdissections of the arteriolosclerotic kidney Oliver [9] found little evidence except in the malignant phase of tubular obstruction by debris with consequent hydro

However there are minute branches (vessels of Ludwig) which extend from the afferent arterioles directly to the tubules These seem to be insignificant in health but according to Oliver and Loomis[illegible] they greatly increase in size and presumably in functional importance when the glomerulus is blocked Oliver's beautiful microdissection studies indicate that such vessels are newly formed in the arteriolosclerotic kidney and by passing the fibrosed glomeruli bring blood directly to the tubules

the glomeruli are shrunken and hyalinized and the tubules atrophic, both being surrounded by connective tissue In more advanced stages these foci are more numerous and coalesce, until finally a stage is reached in which there are only isolated areas of intact parenchyma in these glomeruli and tubules may be hypertrophic, the latter showing evidence of regeneration

The Glomeruli —In most cases of essential hypertension obliteration of glomeruli has been going on for many years by the time they come to necropsy The result is that some fraction of the totality of glomeruli has already been completely destroyed, while others are in various stages of

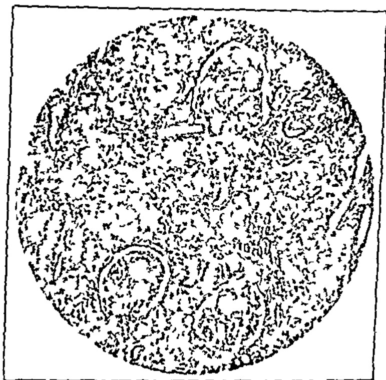


Fig 42 —Hyalinization of glomeruli in the arteriolosclerotic kidney of essential hypertension secondary degenerative changes in tubules (Same kidney as Figure 4 page 287)

the process and still others are completely intact As a rule fewer intermediary pictures are seen than in most instances of glomerulonephritis or the malignant phase of essential hypertension in which the patient is apt to succumb while glomerular obliteration is going on at a rapid rate

The glomerular lesions are consequences of the arteriolosclerosis and follow the latter * By the use of special stains McGregor[4] has shown that

* Whether this statement is invariably true requires further study Sometimes one sees hyalinization within a glomerulus although at least the terminal portion of the afferent arteriole seems little changed The blood supply to such glomeruli should be studied in serial sections to learn whether there is narrowing further up stream Goormaghtigh[23] has made histological observations which he interprets as indicating hyalinization of glomeruli antedating arteriolosclerosis

Microscopically there are found first the same changes as in the benign varieties of essential hypertension consisting in arteriolosclerosis, hyalinization of glomeruli and atrophy of appertaining tubules with replacement fibrosis. The arteriolosclerotic process is of varying degree depending on the duration of the hypertension.

The characteristic feature of the malignant phase of essential hypertension is however the additional presence of *necrosis and endarteritis* of the renal arterioles. The pathogenesis of these acute arteriolar lesions is discussed on page 625. The necrotizing and endarteritic process involves the afferent and interlobular arterioles and may extend into the glomerulus.

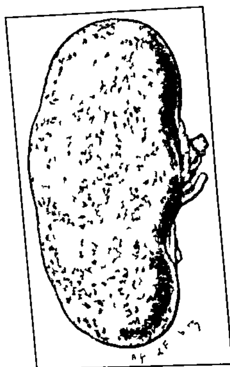


Fig. 43.—Kidney in the malignant phase of essential hypertension. Numerous hemorrhages of varying size; surface almost smooth.

Not all the arterioles are thus affected but sometimes the process is very widespread. The necrotic areas of the walls of the affected vessels are swollen and stain a deeper red with eosin than does an area of hyaline degeneration; often they appear smudgy. The necrotic substance is often distinctly granular. In it the nuclei have either completely disappeared or there is karyorrhexis with scattering of nuclear fragments. Both intima and media may be involved and the various elements of the vessel wall become indistinguishably fused with one another. A very characteristic appearance is often seen when the vas afferens is necrotic at its entrance into the glomerulus, appearing in the hematoxylin-eosin preparation

nephrotic distortion The tubules in intact areas become hypertrophic and show evidences of regeneration if the amount of renal tissue destroyed has been very great Oliver found that the hypertrophy involves especially the proximal convoluted tubule In those cases which had impairment of renal function there are areas of greatly dilated tubules lined by low epithelium These appearances are similar to those which have been described in detail in the chapter on Glomerulonephritis (page 608) However the compensatory hypertrophic changes are rarely as well marked in essential hypertension as in glomerulonephritis The reason for this is probably that only a comparatively small proportion of cases of essential hypertension develops renal insufficiency so that compensation by intact elements is not needed also in essential hypertension the blood supply to even the intact parts is notably diminished by the arteriolar disease

As the specific renal elements atrophy there occurs a replacement fibrosis which in some long standing cases becomes very widespread Round cell infiltrates are not uncommonly present in the interstitial connective tissue Rather exceptionally there is considerable deposition of lipoid in the medullary portions

The lesions of the afferent and interlobular arterioles which initiate the renal changes have already been described (page 284) McGregor[4] found in serial sections that the efferent arterioles are normal However I have repeatedly observed that in patients with both hypertension and diabetes there may be high grade hyalinization of the efferent arterioles

Anatomical Findings in the Malignant Phase of Essential Hypertension — There are very characteristic lesions in the malignant phase of essential hypertension These were first described by Fahr[30] and since then important contributions have been made by Herxheimer[6] Stern[31] Keith Wagener and Kernohan[9] Bell and Clawson[10] Murphy and Grill[32] and Klemperer and Otani The lesions have been exhaustively studied by Dr Paul Klemperer at Mount Sinai Hospital In two years he encountered 12 typical cases at necropsy Through his kindness I have been enabled to study the anatomical preparations of these cases as well as many in subsequent years

The macroscopic picture of the kidneys is often so characteristic that in most cases inspection renders one strongly suspicious of the nature of the histological process before seeing the sections The kidneys are generally of normal size or even somewhat swollen but in other cases there is considerable contraction The surface may be but slightly granular or the granulations may be well marked Evidently both the size and the amount of granulation depend on the duration of the benign period preceding the malignant phase The fundamental color is generally the brownish or grayish red found in the usual case of essential hypertension but in addition the color is variegated by the presence of yellowish areas and of hemorrhages The latter are often very numerous of varying size and frequently of irregular outline Such hemorrhages are extremely uncommon in ordinary essential hypertension and constitute when present in large number the characteristic macroscopic feature of the malignant phase of the disease But they are not present in all instances

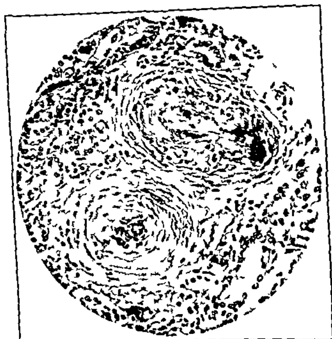


FIG 45 —Two small arteries of kidney in the malignant phase of essential hypertension The upper vessel shows arteriolar necrosis the lower endarteritis with endothelial proliferation

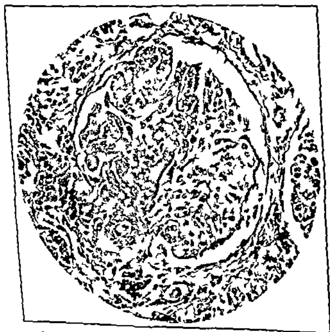


FIG 46 —Necrosis of the vas afferens and its first branches in the malignant phase of essential hypertension

is a deeply red-stained ring which stands out prominently The first divisions of the vas afferens may also be necrotic Thrombosis of the involved vessels is very common

In most, if not all, of the cases there is also well marked endarteritis of the small renal arteries and arterioles It may attain an extreme degree It consists in connective tissue thickening of the intima, endothelial proliferation is frequently well marked There may also be periarterial cellular infiltration this is quite probably a reaction to the regressive changes in the inner layers of the vessel wall (Klemperer) Fatty change

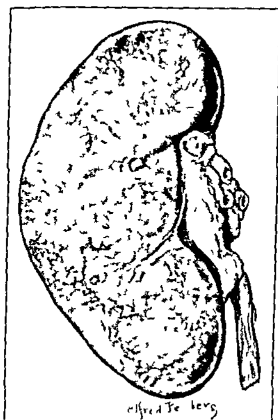


Fig 44 —Kidney in the malignant phase of essential hypertension Fewer hemorrhages than in kidney of Figure 42 marked granulation

may occur in the wall of the affected vessel but Herxheimer[6] states that this is decidedly less marked than in severe arteriolosclerosis Blood may rupture through the necrotic arteriolar wall into the surrounding tissues and there may be small aneurysmatic outpouchings

Some of the glomeruli are atrophic or hyaline as in the benign form of essential hypertension though these lesions are often not widespread In addition, there are changes which resemble those of glomerulonephritis but are not diffuse These consist in moderate proliferation of the nuclei of the tuft as well as of the capsular epithelium It is to be emphasized that they involve only a portion of the glomeruli usually only a small

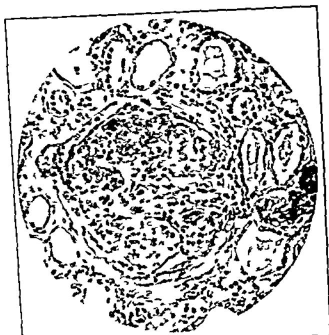


Fig 47 —Necrosis of some glomerular loops in the malignant phase of essential hypertension

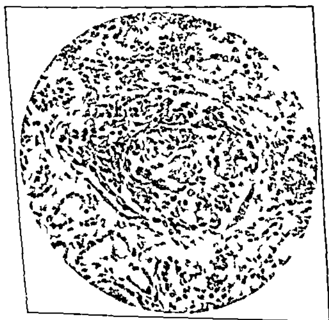


Fig 48 Proliferation of epithelium of glomerular capsule with crescent formation in the malignant phase of essential hypertension

percentage Some of the glomeruli show necroses Most often the necrosis is confined to the first branches of the vas afferens being continuous with the necrotizing process in the wall of this vessel In other instances, the entire glomerular tuft is necrotic with nuclear fragmentation The cause of such necrosis *in toto* of the glomerulus can sometimes be demonstrated to be thrombosis of the afferent arteriole There is often hemorrhage into the capsular space from a necrotic capillary loop

The tubules present the same atrophic and degenerative changes as in the benign forms of essential hypertension In the malignant phase of the disease however owing to the rapidity of the process the degenerative changes in the tubular epithelium are generally much more striking Hyaline droplet degeneration may be especially prominent The tubules often contain blood

In the cases of the malignant phase of essential hypertension that I have seen arteriolar necrosis has occurred though not commonly in organs other than the kidney Among these organs have been the intestine suprarenal gland pancreas and liver but in each instance only isolated vessels have been affected Cohen[34] has observed chorioretinal arteriolar necrosis Klemperer has found endarteritis in a number of cases of the malignant form of essential hypertension in the liver pancreas and other organs Endarteritis seems to be generally if not always present in the small arterial vessels of the retina and choroid when there is hypertensive neuroretinopathy in these cases (See illustrations of Keith Wagener and Kernohan[9]) It was mentioned above that Kernohan Anderson and Keith have found medial hypertrophy in the arterioles of the voluntary muscles in the malignant phase of essential hypertension Necrosis and endarteritis of arterioles or small arteries may produce ischemic lesions in the bowel pancreas brain and other organs I have seen intestinal perforation of this organ and Hranilovich and Baggenstoss[3] observed pancreatic infarcts in 7 and pancreatic focal necrosis in 21 of 100 patients with malignant hypertension

Other Anatomical Findings in Essential Hypertension – While cardiac hypertrophy arteriolosclerosis and the arteriolosclerotic kidney are the lesions most constantly encountered at the necropsy of an individual who had essential hypertension other changes are almost invariably also present These however vary greatly in different instances

Arteriosclerosis of the large arteries is present in the vast majority of instances often in a widespread and severe form This is particularly the case where the hypertension is associated with diabetes or occurs in very old individuals The consequences of such arteriosclerosis of the coronary or cerebral vessels quite often dominate the clinical picture in such instances myocardial degeneration or areas of softening in the brain are found Or the combination of the hypertension and cerebral vascular disease may have led to cerebral hemorrhage Arteriosclerotic changes in the choroid and retina are common There is generally well marked or severe arteriosclerosis of the aorta and its branches but in other cases these vessels show little more atheromatous change than is usual at the age of the patient Arteriosclerotic gangrene of the extremities is rare except if the hypertension is complicated by diabetes Arteriosclerotic lesions of

cases of arteriolosclerotic kidney (i.e. essential hypertension) during the time that there were 98 cases of chronic glomerulonephritis.

It seems highly probable that essential hypertension is increasing in frequency for the progressive rise in the expectancy of life results in more individuals attaining the age period in which essential hypertension occurs. It is also widely held that the greater stress and strain of modern life predisposes to essential hypertension. Another belief that has attained considerable currency is that essential hypertension is more common among the well-to-do and professional classes than among the poor. It does not seem to me that this last point has been adequately demonstrated. I have observed that the incidence of essential hypertension is high among dispensary patients, particularly among women at or past the menopause. Certainly if worry and other forms of emotional strain are contributory factors in the genesis of essential hypertension, this class of poor women should have its full share and more of the disease. In the next paragraph it will be mentioned that urban negroes, whose whole life is a struggle with poverty, have a high incidence of hypertension. Hashimoto[4] *et al.* found among urban Japanese that hypertension is more frequent in poor than in pay patients and that it appears at an earlier age in the former.

RACE AND ESSENTIAL HYPERTENSION

Race is apparently a factor that influences the incidence of essential hypertension. From the scanty information available the latter appears to differ among various peoples. However, it has not been established that the differences in incidence of essential hypertension between ethnic groups is a specific function of their race rather than of the conditions under which they live. In the question of the relation of race to essential hypertension there is suggestive evidence for two correlations.

1. Essential hypertension appears to be less common in those peoples in whom the normal blood pressure averages low. Harris[5] and others have found that essential hypertension is rare among Chinese and other oriental peoples who normally have a lower blood pressure than occidental Caucasians. Smirk[7] summarizes evidence indicating that both the normal blood pressure and the incidence of essential hypertension are low among the Filipinos, Puerto Ricans, the poorer classes in India and the Yucatan, Cuna and Zuni Indians. Kean's[8] careful studies reveal that in Panama the West Indian negroes have a higher normal blood pressure than the Panamanians and about seven times as high an incidence of hypertension. Among Indians in the Southwest of the United States who live largely a reservation existence, Cohn[9] observed the incidence of hypertension to be only 0.96 per cent. In Mexico likewise Chavez[10] found a low incidence of hypertension among Indians. In New York City I have found the incidence of essential hypertension among Puerto Ricans low.

2. There is some evidence that peoples living under primitive conditions have little hypertension. Nye[11] found hypertension completely absent in the Australian aborigine. Donnison[12] noted that hypertension scarcely occurs in negroes living in a primitive state in Kenya Colony; he encountered only two questionable instances among them. Contrariwise, essential hypertension is very common in negroes living in large cities in the

Chapter

25

ESSENTIAL HYPERTENSION II ETIOLOGY AND PATHOGENESIS

THE nature and causation of essential hypertension have been the object of a great number of clinical, post-mortem, experimental and genetic studies ever since the frequency of the disorder—rivaled only by arteriosclerosis, which it so often overlaps, among lethal maladies—became clear early in this century. With the experimental production of hypertension by Goldblatt the tempo of investigation became accelerated. Many facts have been established and a number of theories based on accurate observation and experimentation propounded. Nevertheless *neither the cause nor the nature of essential hypertension are understood*. Indeed what is labeled essential hypertension doubtless includes more than one nosologic entity. The immediate mechanism of the rise in blood pressure is augmented contraction of the arterioles. But what increases the contraction of the arterioles in essential hypertension remains a mystery. At present theories regarding essential hypertension as primarily a psychosomatic disorder, an aberration of the endocrine glands, or a consequence of renal arteriolar sclerosis or other kidney disease hold the center of the stage. The possibility exists that each of these explanations may hold in still *undifferentiated conditions grouped under essential hypertension* and they may not be mutually exclusive. But as yet none of the conceptions of the nature of essential hypertension is more than a theory, perhaps not more than a working hypothesis.

THE FREQUENCY OF ESSENTIAL HYPERTENSION

Essential hypertension and its consequences are among the most common conditions confronting the practitioner. Among 7,872 private patients Janeway[1] found that 870, or 11.1 per cent, had systolic blood pressures of 165 mm. or more, the large majority being instances of essential hypertension. In Romberg's[2] private practice 24.8 per cent of all organic heart disorders were due to hypertension. Fahr[3] calculates that 140,000 deaths in the United States in 1924 were due to hypertension or its consequences, this being 23 per cent of all deaths in persons over fifty years of age. Bell's[4] autopsy findings indicate that about 13 per cent of individuals past fifty years die of hypertensive disease. These figures afford some indication of the importance of essential hypertension to the physician, a fact which has been adequately realized only within recent years.

Essential hypertension is far more frequent than nephritic hypertension. Of 82 instances of hypertension which I studied at necropsy, 72 were essential and only 10 nephritic. On Romberg's service there were 696

as in the North However Spitzer[19] found a high incidence of hypertension in Curaçao which is very hot

AGE AND ESSENTIAL HYPERTENSION

Essential hypertension only exceptionally produces symptoms before the declining phase of life To how early an age its roots extend will be discussed below but it is certain that in the vast majority of instances the clinical manifestations of the disease first appear after the age of forty years Janeway[1] found that the three decades from forty to sixty nine include between 80 and 90 per cent of the cases Though their youngest patient was only thirteen years of age Bell and Clawson[20] found that 90 6 per cent of 417 cases of essential hypertension were over forty years of age at the time of death However essential hypertension is so enormously frequent a disease in the United States that even the small proportion of cases producing clinical symptoms between the ages of thirty and forty render incapacitating illness due to essential hypertension during this decade quite common Nowadays large numbers of cases of essential hypertension under the age of thirty are detected in military and routine examinations but it is rare for the disease to produce symptoms at this time of life unless they are engendered by fear of high blood pressure However even in early childhood there are rare cases of essential hypertension which produce symptoms and even prove fatal Above was mentioned a case of essential hypertension which went into the malignant phase and succumbed at the age of eight and a half years Holzmann[1] has described essential hypertension in a boy aged four and a half years Hutchison and Moncrieff[22] observed a boy aged eight and a half years whose blood pressure was 210/150 mm at necropsy the kidneys were found normal So far as I am aware the youngest sufferer from essential hypertension on record is the colored boy aged two years reported by Taussig and Remsen[23] with a blood pressure of 195/135 mm at necropsy the kidney showed but slight changes Sobel[24] found in the literature slightly less than 100 cases of essential hypertension in children and reported 7 of his own However these were probably not all cases of essential hypertension Sobel s first case had precocious puberty and may have had disease of the adrenal cortex

The following table gives the age and sex incidence of 96 cases of chronic hypertension which were shown at necropsy not to be due to glomerulonephritis or pyelonephritis

Age at death years	*Number of cases*	
	Male	*Female*
0 to 29	2	0
30 to 39	2	4
40 to 49	5	14
50 to 59	18	16
60 to 69	10	14
70 to 79	3	6
80 to 89	1	0
91 to 99	0	1
Total	41	55

United States In New York City, I have observed that hypertension is more common in negroes than in whites and that extreme degrees of hypertension are much more frequent in the negro In Cincinnati Allen[13] found hypertension more than twice as common in negro factory workers than in their white companions Flaxman[14] noted in Chicago that hypertensive heart disease is more common in negroes (I have also observed that the proportion of cases of essential hypertension in which the clinical picture is dominated by heart failure—not angina—is higher in colored patients perhaps because of their strenuous occupations) According to Weiss and Prunty[15] hypertension tends to occur earlier in the negro In another group of negroes residing in the midst of "civilization" the South African Bantus Ordman[17] found a high incidence of hypertension Dubois[16] observed systolic hypertension (he measured only the systolic pressure) in the Congo I do not know the state of their culture or their relations to the Caucasian settlers

Blackford[18] quotes Firestone as finding that the Eskimos have approximately the same incidence of hypertension as occurs in the United States

In New York City I have found that essential hypertension is more common in Jews of the poorer groups than among Gentiles of corresponding economic status but have not noted such a difference among the well to-do I have observed that the ratio of essential to nephritic hypertension is much higher among Jews than among Gentiles this difference is also due to the lower incidence of glomerulonephritis among Jewish than other, especially Italian and Irish children

The explanation for the differences in incidence of hypertension in various races is not at hand Genetic factors, differences in occupation diet and mode of life are among the factors that must be taken into consideration Further study of comparative pathology is highly desirable in the hope that it may throw light on the importance of genetic factors in hypertension and perhaps elucidate the importance of diet of psychosomatic influences and of a so called "civilized" environment in producing high blood pressure If it is proved that the incidence of essential hypertension rises with civilization the problem then arises of unveiling whether it is the diet complicated interpersonal relationships or other aspects of our way of life that is guilty The explanation of why the negro in his primitive environment in Africa has little hypertension while it is among the most common afflictions of the American negro may well be a clue to the nature of essential hypertension

An excellent bibliography of the incidence of essential hypertension in different races is given by Bays and Scrimshaw[407] They conclude that racial differences do exist but the available data are inadequate to differentiate the importance of genetic psychologic and social factors (the authors it seems to me overestimate the importance of the influence of arm size in determining racial differences)

Climate —More information is needed regarding the relation of climate to essential hypertension Some evidence that tropical climate tends to lower normal blood pressure is cited on page 267 I have the impression without supporting statistical evidence that essential hypertension is not as enormously frequent among whites in the far South of the United States

SEX AND ESSENTIAL HYPERTENSION

Essential hypertension is a common disease in both sexes. There have been differences of opinion whether essential hypertension is more common among males or females because few series include all types of clinical material. Janeway[1] found hypertensive disease to be 15.6 per cent more frequent in males. However, his patients included no gynecological cases, which probably eliminated some of the very common instances of essential hypertension following the menopause. Bell and Clawson found essential hypertension 1.4 times as common in males. On the other hand, two-thirds of Boas and Fineberg's[9] 236 cases of essential hypertension were in women. Blackford, Bowers and Baker[20] also found hypertension twice as often in females. In dispensary practice I have also observed essential hypertension to be more common in females. At necropsy Bell[11] found no significant sex differences in the deaths from hypertension up to the age of fifty, but after that there were 14.1 per cent of deaths from hypertension in males and 11.9 per cent in females. To the writer it seems that the reason for the greater clinical incidence of hypertension in females is that the disease lasts longer in them, especially because of the smaller incidence of coronary disease.

HEREDITY AND CONSTITUTION IN ESSENTIAL HYPERTENSION

Heredity. — It was already known to Morgagni[2] that there is a marked predisposition in certain families to cerebral hemorrhage, which is in the vast majority of instances an accompaniment of hypertension. Demonstration of the hereditary and familial occurrence of essential hypertension is rendered more difficult by the fact that the disease usually first becomes clinically manifest in middle or late life, so that the parents and many other relatives of the patient are not available for examination. It is probably for this reason that Janeway underestimated the significance of heredity in essential hypertension.

In recent years, however, there have been published many individual observations and statistical investigations which show that the hereditary factor in essential hypertension is very striking, and that there is a marked tendency for the disease to occur not only in successive generations but also in several brothers and sisters of a single generation. Thus Rosenbloom[32] observed a family in which both parents died of cerebral hemorrhage; of their 10 children 8 already have hypertension, only the 2 youngest (aged thirty-three and thirty-five years) not as yet having any elevation of blood pressure. Allbutt[34] mentions a man with hypertension whose paternal ancestors for three generations died of cerebral hemorrhage, a total of four generations. Nikitis[35] was able to trace the predisposition to arterial hypertension through three generations of the families of 32 hypertensive patients. O'Hare, Walker and Vickers[36] elicited a family history of vascular disease in 68 per cent of 300 patients with hypertension, but in only 37.6 per cent of 457 controls. Most practitioners are acquainted with families the members of which are subject to "strokes."

The cases under thirty years of age were in a man, aged twenty three years, with a tumor of the suprarenal cortex and in a youth aged sixteen years with hypothyroidism. In this series there were thus no cases of essential hypertension which proved fatal before the age of thirty. The table indicates that eighty per cent of fatalities in patients with essential hypertension occur between the ages of forty and sixty nine.

The above figures refer to the clinical incidence of essential hypertension, *i. e.* to individuals whose blood pressure is measured when they come to the physician or hospital because of illness. In recent years however measurements of the blood pressure of those who believe themselves healthy have made it evident that *the roots of the disease extend to a much younger period of life.* The enormous number of blood pressure determinations carried out nowadays on seemingly healthy persons in conjunction with military service, insurance, industrial employment, college admission, etc. disclose that a higher proportion than was previously realized have a blood pressure above the normal for the age. Alvarez[5] found that 20.7 per cent of seemingly healthy male college students and 2.7 per cent of female students have a systolic pressure above 140 mm. In a similar investigation Diehl and Sutherland[6] showed that a large proportion of these elevations are transitory, being due largely to the emotional impact of the examination. These authors found an incidence of 5.6 per cent of permanent or transitory hypertension among male college students. In the past there was a tendency to discount the significance of such transitory hypertension occurring only under the emotional stress of an insurance or military examination and followed by repeated normal readings when the patient became accustomed to the examiner. However, the writer has for many years been convinced that *at least the larger moiety of individuals exhibiting such transitory emotional hypertension ultimately prove to have essential hypertension,* although it may be decades before this is evident. For example the author recently saw a man of thirty nine years who was considered to have developed essential hypertension only within the past year, but who gave the information that when his mother consulted a famous student of hypertension for essential hypertension thirty years before, this clinician had measured his blood pressure and predicted that some day he would have his mother's disease. The history is often given by patients with essential hypertension that when they were young—in the teens or twenties—an examiner had been suspicious of high blood pressure but had failed to confirm his suspicion on subsequent examinations. In a study of the medical records of over 22,000 Army officers Levy[7] *et al.* found that sustained hypertension developed more frequently in those who previously had transitory hypertension. And Hines[8] showed that individuals whose blood pressure is in the upper range of normal often show manifest essential hypertension ten or twenty years later, while this rarely develops in those with low normal pressures. Early appearance often in the teens of the precursory manifestations of essential hypertension is especially apt to be found when both parents are hypertensive. All these observations indicate that the actual onset of essential hypertension occurs long before the disease becomes manifest (*cf.* also page 758).

The hereditary factor in essential hypertension was first extensively studied by Weitz[37] He found that among 82 patients with essential hypertension 63 or 76 8 per cent had lost at least one parent from consequences of hypertension Among the remaining 19 patients hypertension seemed probable in 1 brother or sister of 10 and in 2 brothers or sisters of 3 In only 6 of the 82 hypertensive patients was no family history of the disease obtained Among 267 controls only 30 3 per cent had lost a parent from the consequences of hypertension Weitz found further that about one-half the brothers and sisters of all older patients with essential hypertension also had high blood pressure He observed female twins (from one ovum) aged sixty three years both of whom had marked hypertension (178 and 182 mm systolic) though one had led a hard life working in a factory and the other had been comfortably situated As a result of his investigations Weitz concludes that essential hypertension is inherited as a dominant characteristic though he admits that the dominance is not invariably demonstrable Hines[38] likewise adduced evidence that essential hypertension is inherited as a dominant characteristic He found that a family history of hypertension is five times as frequent among hypertensives as among controls In a careful study Ayman[39] found that in families in which both parents had normal blood pressure only 3 1 per cent of the children had high blood pressure while the latter was present in 28 3 per cent of the children of families with one hypertensive parent and 45 5 per cent of children of two hypertensive parents In a genetic investigation on 2 762 relatives of 186 patients with essential hypertension using modern statistical methods Sobye[40] brought strong evidence that essential hypertension is inherited as a Mendelian dominant Platt's[41] findings indicate the same

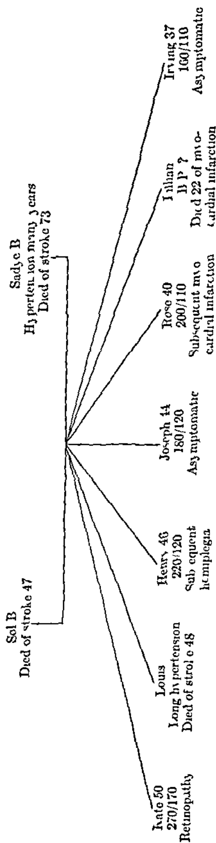
Investigations on *twins* have also brought evidence of the importance of a genetic factor in essential hypertension From his surveys of 31 pairs of monozygotic twins with hypertension Sobye finds that concordance occurs so often in proportion to discordance as to argue strongly for a hereditary factor

Now that determination of the blood pressure had been a routine part of the usual medical examination for over thirty years the writer has had frequent opportunities to obtain evidence regarding the blood pressure of the siblings parents and even grandparents of hypertensive patients The data thus obtained as well as the literature above summarized have convinced me that *no fact relevant to the nature of essential hypertension is as well established as the fundamental importance of heredity*

Parenthetically it may be remarked that arterial hypotension like hypertension may be a familial characteristic Garvin[42] observed 6 instances of hypotension in a family In families predisposed to tuberculosis the blood pressure is apt to be low though exceptions to this are not uncommon

Constitutional Peculiarities —In view of the strong hereditary element in essential hypertension considerable attention has been paid in recent years to general constitutional peculiarities and bodily habitus in relation to the disease Draper[43] has investigated the shape of the chest and profile of hypertensive patients It was mentioned above that Larimore[44] found

I observed almost all the members of the following family



For excellent discussion of the constitutional and hereditary aspects of essential hypertension the reader is referred to the studies of Williams and Sobye[50]

THE RÔLE OF THE KIDNEY IN ESSENTIAL HYPERTENSION

Ever since Richard Bright pointed out that disease of the kidneys may bring cardiac hypertrophy in its wake there have been those who regard all persistent high blood pressure as renal in origin But when the clinical picture now known as essential hypertension was split off from the other forms of Bright's disease many veered to the conception that this variety of elevation in arterial pressure is not caused by renal disease This opinion for it was no more was largely founded on the observation that many patients have high blood pressure despite negative urine and a normal outcome of all tests of kidney function It was not based on anatomical desiderata for the exclusively post mortem morphological data available at the time (say 1925) were generally interpreted to indicate the presence of an abnormal degree of renal arteriolosclerosis in practically all chronic hypertensives However when in 1934 Goldblatt (cf Chapter 10) published his experimental production of chronic hypertension by constriction of the renal artery the debate whether essential hypertension is of renal or nonrenal origin appeared to many to be decided in favor of the former

Considerations Favoring the Renal Origin of Essential Hypertension – 1 There is indubitable clinical and experimental proof that disease of the kidneys can produce chronic hypertension (Chapter 10)

2 While patients with essential hypertension start with negative urine and faultless kidney function most of them ultimately develop proteinuria and many impairment of renal function perhaps 7 per cent succumb to uremia

3 The first measurements of renal blood flow in essential hypertension revealed decreased flow in most of the cases (Coldring[61] *et al*)

4 The large majority of patients with essential hypertension reveal at necropsy well marked renal arteriolosclerosis And in some of the cases in which the small vessels are not sclerotic narrowing of the main renal arteries has been observed (Blackman[2])

5 By means of his clamp Goldblatt produced in dogs and other animals hypertension without change in the urine or impairment of renal function Such hypertension with normal urine and kidney function seemed to be a precise reproduction of human essential hypertension Moreover in simulation of the chronicity of the human disease Goldblatt maintained his dogs with hypertension and good renal function for over seven years and by suitable tightening of the clamp was able to throw them into the malignant phase in a fashion reminiscent of the disastrous change in the clinical course which occurs in human hypertensives (Chapter 26)

The foregoing obviously constitutes strong clinical and experimental support for the doctrine of the renal origin of essential hypertension The thesis is still maintained vigorously and ably by Goldblatt and others

that the blood pressure is on an average higher in healthy factory workers of sthenic bodily habitus than in those of asthenic build. Similarly, most patients with essential hypertension are of a distinctly sthenic bodily habitus. They have a heavy skeletal framework, originally a good musculature, though this is often undeveloped because of a sedentary life, a broad and deep chest and a marked tendency to obesity—for which reason they have been described as of the "musculo-digestive" habitus. Quite commonly (in 71 per cent of the cases according to Muller and Parissius[45]) they are short and stocky with a short thick neck. The investigations of Robinson and Brucer[38] reveal that individuals of broad (sthenic pyknic) body build are much more susceptible to essential hypertension than are those of linear (asthenic leptosomic) habitus. They separated the two groups for statistical analysis by the ratio of the circumference of the chest to the height. They found that men of broad body build have more than four times the incidence of systolic hypertension and seven times the incidence of diastolic hypertension than do those of slender constitution. Robinson and Brucer observed that women of sthenic habitus had 11 times the incidence of systolic hypertension and eight times that of diastolic hypertension.

Patients of sthenic bodily habitus are so much more liable to essential hypertension that one should be especially careful to rule out primary renal disease in a distinctly leptosomic individual with high blood pressure. Glomerulonephritis is more common in persons of asthenic habitus. However, one does occasionally encounter essential hypertension (proved at necropsy) in women of frail asthenic body build.

Essential hypertension is very apt to be accompanied by obesity or diabetes or both. Very often other members of the family of hypertensive patients suffer from these disorders. In countries in which gout is prevalent, this disease is frequently found either in the hypertensive patient or his family. On the other hand, tuberculosis is decidedly less frequent in those with essential hypertension than in the general population (Maurice Fishberg[47]). And when hypertension and tuberculosis are associated, the latter disease is generally of the fibroid type with little tendency to progression. Apparently the constitutional type which is predisposed to essential hypertension is relatively immune to tuberculosis.

Other constitutional peculiarities of individuals with essential hypertension have been described. Thus the investigation of Wiechmann and Pal[48] on the blood groups of individuals with essential hypertension revealed a relative predominance of groups 3 and 4. Backer[49] states that hypertension is rare in individuals with spontaneously appearing hernias, a condition which he considers indicative of low "tone" of the mesodermal tissues. And Quinan[50] found that hypertension occurs with greater relative frequency in left-handed than in right-handed persons. Should these investigations be confirmed, they may open up an interesting line of investigation of the constitutional variant which is unquestionably important in the genesis of many instances of essential hypertension.

Peculiarities in the psychic characteristics of some individuals with essential hypertension will be discussed below.

rather in better accord with the view that renal arteriolar sclerosis is a process that develops with advancing age in many normotensives (page 288) but is enormously accelerated and intensified by hypertension that primarily results from another cause. But it seems plausible that as renal arteriolar sclerosis develops in the course of essential hypertension it augments the high arterial tension through whatever is the mechanism operating in the Goldblatt experiment.

Renal Pressor Mechanisms in Essential Hypertension.—There have been repeated attempts to learn whether the various pressor mechanisms studied in renal hypertension (Chapter 10) operate in essential hypertension.

Renin Angiotonin.—There is no conclusive proof that the renin angiotonin pressor system participates in essential or any other chronic form of hypertension, and much that speaks against it. The evidence in this regard is summarized in Chapter 10 and need not be repeated here. It may merely be reiterated that, despite repeated attempts, circulation of angiotonin has not been unequivocally demonstrated to be responsible for the elevation of blood pressure in essential hypertension.

Shorr's VEM and VDM.—Another mechanism that has recently been considered in conjunction with the pathogenesis of essential hypertension is displacement of the equilibrium between Shorr's VEM and VDM in favor of the former, which is formed in the kidney (page 331). Shorr[46] and his associates have brought forward evidence that there is a similar derangement of the VEM VDM mechanism in essential hypertension in man and renal hypertension produced in the dog by the Goldblatt clamp. In both essential hypertension and chronic experimental renal hypertension they find a balanced increase in the blood of both VEM and VDM. They showed that while normal canine and human kidneys form VEM only under anaerobic conditions, kidney slices which have been kept in an atmosphere of nitrogen for an hour then form VEM aerobically, and that the same is true of both slices from the kidney of a Goldblatt dog and from biopsy specimens of the kidney of patients with essential hypertension removed at sympathectomy. Zweifach, Black and Shorr[47] were also able to demonstrate a histochemical manifestation of this metabolic change in the kidney by the use of a tetrazolium salt which is reduced by intracellular dehydrogenases to a deep red, water-insoluble formazan. They found that in Goldblatt dogs, in biopsy specimens of the kidney in human essential hypertension and in normal kidney slices which had been kept in nitrogen for an hour—all conditions in which VEM is formed aerobically as well as anaerobically—there is the same characteristic distortion of the pattern of the red formazan deposits in the proximal convoluted tubule cells, which differs sharply from the formazan distribution in the normal tubule cell. By catheterization of the hepatic and renal veins in normal and hypertensive humans, Shorr and Zweifach could demonstrate no or mere traces of VEM and VDM in normals, but in hypertensives there was a large amount of VEM in the renal blood and of VDM in the hepatic blood. Shorr's studies appear to have demonstrated abnormality in the VEM VDM mechanism in essential hypertension. But whether this abnormality plays a part in the pathogenesis of the disease remains to be demonstrated.

However, none of the lines of evidence just sketched has proved unequivocal, and they may be countered individually as follows.

Considerations Opposing the Renal Origin of Essential Hypertension.—

1. Chronic hypertension may be produced in man by other than renal causes. This is shown by hypertension in suprarenal tumor, which is cured by ablation of the growth.

2. Many, albeit not the majority, of patients with essential hypertension have high blood pressure for a decade or more without developing proteinuria, and renal function becomes sensibly impaired in only a small proportion.

3. While the pioneer study of renal blood flow in essential hypertension by Goldring *et al.* disclosed diminution in most cases, they also obtained normal results in some instances. The same is true of the other alterations in renal hemodynamics that occur in essential hypertension (page 807). Talbott[53] and his associates compared renal clearances with biopsy findings in essential hypertension. They found that when there is little or no arteriolosclerosis, renal blood flow, glomerular filtration and the filtration fraction are normal. Only with the development of renal arteriolosclerosis do blood flow and filtration diminish. These findings are difficult to reconcile with the theory that decrease in renal blood flow is primarily responsible for essential hypertension. In his recent excellent survey of the renal circulation in essential hypertension, Chasis[54] reaches the conclusion that the alteration in renal hemodynamics is a sequel rather than the cause of essential hypertension.

4. Patients may have essential hypertension for years without demonstrable renal arteriolar sclerosis. This is shown by the biopsy studies of Smithwick and Castleman (page 677). Moreover, even necropsy material shows a not inconsiderable proportion of cases in which renal arteriolar sclerosis is no more pronounced than in many normotensive individuals of the same age (page 288). And significant narrowing of the main renal artery and its first branches is, in my experience, at least a very great rarity. That blood flow through the kidneys in essential hypertension is not always decreased by organic thickening of the arteriolar walls is also indicated by the finding of Cox and Dock[55] that postmortem perfusion of the kidney meets with little more resistance in some cases of essential hypertension than in normotensive controls of the same age. Also pointing in the same direction is the finding of Goldring *et al.* that the increase in renal blood flow in the pyrogenic reaction is of the same order of magnitude in normals and patients with essential hypertension.

5. Hypertension can be produced in both humans and experimental animals by other than primarily renal mechanisms. This is shown by the hypertension that may complicate the therapeutic administration of desoxycorticosterone acetate, cortisone or ACTH. It is possible that the kidney may participate in the mechanism of the hypertension, but the primary cause is the administration of the hormone.

To the writer it appears that the preponderance of evidence as just summarized is against the theory that the elevation of blood pressure in essential hypertension is primarily a consequence of renal arteriolar sclerosis or decrease in renal blood flow of other origin. The evidence seems,

de Wesselow and Griffiths[65] Later Page and others revealed no evidence that such is the case Nordal Capps[66] and his associates find an abnormally high content of pressor substance in the urine of hypertensive subjects Testing alcoholic extracts of blood and urine on cats von Euler and Sjostrand[67] obtained less pressor effect from hypertensive patients than from normals (cf also page 325)

Prinzmetal[68] and his coworkers and Pickering[69] attacked the problem of a circulating pressor substance in essential hypertension by transfusing blood from hypertensive subjects into individuals with normal blood pressure By cross-transfusions of as much as 2000 cc —with the result that as much as 42 per cent of the circulating blood volume of the individual with normal blood pressure was derived from the person with hypertension—they were unable to produce rise in blood pressure Goldman[70] and his associates observed slightly more rise in diastolic pressure when they transfused into hypertensive patients arterial blood from other hypertensives than when normotensive blood was given but the differences do not seem significant to me

The numerous but as yet inconclusive attempts to demonstrate the circulation in chronic hypertension of angiotonin and other pressor substances derived from the kidney have been discussed in Chapter 10

Recently Schroeder[71] and his coworkers have found in the blood in both renal and nonrenal hypertension a vasoconstrictor and pressor substance which they have termed *pherentasin* They did not find it in normotensive blood The concentration of pherentasin and the diastolic pressure were not correlated The significance of pherentasin remains to be demonstrated

It is thus evident that the circulation of a pressor body in essential hypertension has not yet been demonstrated However the available data do not rule out the presence of such a pressor substance The failure to demonstrate it in the circulating blood may be due to technical inadequacies just as various hormones which circulate have not yet been isolated from the blood

Another hypothetical possibility that immediately comes to mind is that in essential hypertension the target organ i e the arterioles—is sensitized to normally circulating pressor bodies However there is no evidence for this conception Judson[72] and his associates found no increase in the sensitivity of hypertensive patients to intravenous injections of either epinephrin or arterenol And Page and McCubbin's[73] observations indicate that the reactions to vasoactive drugs in various forms of experimental hypertension do not depend on intrinsic changes in the muscle of the vessels

The problem of intrinsic change in the arterioles in hypertensive diseases has been attacked in another way by Tobian and Binion[74] They find the sodium and water concentrations are increased in the renal artery and psoas muscle of human hypertensive subjects These investigators also find an increase in the water content of the aorta of the hypertensive rat They speculate that swelling due to similar increase in the salt and water of arteriolar *muscle might* narrow the lumen sufficiently to produce hypertension The speculation is an interesting one and merits further study

It should be remembered that VEM is not itself a pressor body but one that is demonstrated by increased vasomotion and reactivity to epinephrin (and perhaps sympathin or a similar substance) of certain small blood vessels in the rat's mesoappendix.

The Juxtaglomerular Apparatus.—On page 336 it was seen that secretion of a pressor body by the juxtaglomerular cells has been suggested as the mechanism of essential and other forms of hypertension, but that there is no persuasive evidence in favor of this conception.

The Intrarenal Pelvis.—Ravich[58] reported that a high proportion of patients with essential hypertension have a pelvis situated entirely with the renal parenchyma (intrarenal pelvis) and suggested the possibility that in such individuals minor obstructive uropathies might result in renal ischemia and consequent hypertension. However, Hyman and Schlossman[59] found no greater incidence of intrarenal pelvis in hypertensive patients than in normotensive controls.

None of the studies just surveyed shows that essential hypertension results from disease of the kidney or its blood vessels. However, they also do not disprove the renal origin of the disease. It is pertinent in this connection that, even though the hypertension produced by the Goldblatt clamp is certainly renal in origin, the actual mechanism of its production is unknown; we do not even know if it is due to elaboration of a pressor body by the kidney or deficiency of an antipressor principle normally formed by the organ, or both. In the light of this ignorance of the mechanism of renal hypertension, until either this mechanism or the nature of essential hypertension is unveiled, one can not be sure that the latter is not of renal origin. But as yet the available evidence does not indicate even with probability that the origin of essential hypertension lies in the kidney.

CIRCULATING PRESSOR SUBSTANCES IN ESSENTIAL HYPERTENSION

Efforts to elucidate the nature of essential hypertension have naturally included attempts to demonstrate the circulation of a pressor body. Deficiency of a normally circulating antipressor substance also furnishes a conceivable mechanism of hypertension.

Early attempts to demonstrate a pressor body in the blood were concerned with epinephrin, but apart from hypertension due to chromaffin tumors, the search was unsuccessful (page 70[illegible]). Interest in the Cushing syndrome led to attempts to demonstrate pitressin in the blood and cerebrospinal fluid, but the studies of Page[60] and Hoyle[61] showed that in essential hypertension these fluids contain no excess of pitressin. While Henriques and Henriques[404] found the antidiuretic activity of the serum in essential hypertension a little higher than in normals, the differences are not striking.

A number of investigators have thought that they could demonstrate by experiments with strips of artery, perfusion of organs, or injection into animals that the blood of individuals with essential hypertension possesses abnormally strong vasoconstricting properties (for literature see Leiter[62]). However, careful investigations by Curtis, *et al.*,[63] Wakerlin and Brunner,[64]

But hyperglycemia is present in only a portion of cases of essential hypertension—from 10 to 30 per cent according to Herrick[85] less commonly according to Gelmann[86]—and there is no parallelism between the glycemia and the blood pressure even in the same patient. The relations between hyperglycemia and hypertension are further considered in the section on Diabetes in Essential Hypertension.

4 In Addison's disease the blood pressure is very low. It is to be remarked however that it has by no means been demonstrated and is even improbable that the hypotension of Addison's disease is the result of diminished elaboration of epinephrin; it is more than doubtful that the normal arteriolar tonus is dependent on the epinephrin content of the blood.

5 Schur and Wiesel[7] thought that they had demonstrated the presence of an excess of epinephrin in the blood of hypertensive patients because the serum of such individuals even in considerable dilution caused dilatation of the pupil of the enucleated frog's eye (Meltzer Ehrmann reaction). However O'Connor[88] and others have shown that the reaction is not specific for epinephrin but is given also by substances formed during the coagulation of the blood. Janeway and Park[89] avoided this error by testing the effect of plasma in causing contraction of a strip of surviving artery. With this technique they were unable to demonstrate the presence of epinephrin in the blood of 6 patients with hypertension. Using a biological test for epinephrin so delicate that it revealed the presence of the substance in a dilution of 1 to 700 000 000 Huelse[90] was unable to find epinephrin in the venous or arterial blood of individuals with either nephritic or essential hypertension. The method was so sensitive that it revealed epinephrin in the blood of the suprarenal vein and as far in the circulation as the right heart though no further. Kobro[91] has developed a quantitative chemical method for determining epinephrin in the blood. With this method he found the epinephrin content of the venous blood in essential hypertension in the same range as in normotensives (22 to 79 millig mm is per ml).

The failure of such extremely delicate methods to reveal an increase in epinephrin in the blood of hypertensive patients seems fatal to the once promising theory that essential hypertension is produced by an excess of epinephrin in the blood— the beautiful dream of adrenalinemia as Janeway[89] called it. Smaller quantities of epinephrin than those demonstrable by these methods could have no appreciable pressor effects. Moreover the demonstration by Beer King and Prinzmetal[93] of epinephrin in the peripheral blood of a patient with paroxysmal hypertension due to a tumor of the suprarenal medulla shows that present methods suffice to detect epinephrin when this substance circulates in concentration sufficient to produce hypertension (see page 932).

Two other lines of evidence that hyperepinephrinemia is not responsible for the elevation of blood pressure in essential hypertension have been brought out in recent years especially through the investigations of Goldenberg[94] and his associates.

(a) On intravenous infusion of epinephrin into normotensives at a rate producing elevation of systolic pressure to about 180 mm Goldenberg and his associates found greatly increased cardiac output little change in diastolic pressure sharp drop in peripheral resistance rise in mean pulmo

THE ENDOCRINE ORGANS AND ESSENTIAL HYPERTENSION

In recent years, there has been extensive investigation of the relations of abnormalities in the function of the endocrine glands to alterations in blood pressure, and many have thought, with much reason that at least part of the solution of the riddle of essential hypertension lies in a perversion of the internal secretions

THE ADRENAL GLANDS

Various theories incriminate both suprarenal medulla and cortex in the pathogenesis of essential hypertension In the case of the medulla hypersecretion of epinephrin and more recently of nor-epinephrin, is the suggested mechanism With expanding knowledge of the cortical steroids study of perversion of adrenal cortical function has moved toward the center of the stage in the investigation of essential hypertension

The Theory of Hyperepinephrinemia —In view of the fact that the medulla of the suprarenal gland secrets the most powerful pressor substances known it is a rather obvious thought that hypertension may result from increased function of this organ Indeed immediately after the discovery by Oliver and Schaefer[75] of the pressor properties of extracts of the suprarenal medulla Neusser [6] described two cases of hypertensive disease in young adults terminating by cerebral hemorrhage in which carcinoma' of the suprarenal gland was found but no disease of the kidneys He believed the hypertension in these cases to be due to secretion of the pressor substance of the suprarenal gland by the tumor But the actual founder of the theory that hypertension results from increased secretion of epinephrin was Vaquez [77] who observed a frequent coincidence of suprarenal hyperplasia and hypertension The following lines of evidence have been adduced in the effort to demonstrate that hypertension is the result of increase in the epinephrin content of the blood

1 Chromaffin tumor of the suprarenal medulla (pheochromocytoma) may produce high blood pressure The hypertension may be paroxysmal or continuous the latter closely mimicking classical essential hypertension (*cf* page 933)

2 Wiesel [78] Parkinson [79] and others claimed to have observed hyperplasia of the suprarenal medulla in hypertension On the other hand analyses of suprarenal glands from hypertensive subjects by Elliott[80] and Ingier and Schmorl[81] did not show them to contain more epinephrin than the suprarenals of individuals with normal blood pressure Mullon[82] noted hyperplasia of the chromaffin tissue outside of the suprarenal gland (paraganglia) but so far as I am aware this has not been confirmed Parenthetically it may be mentioned that Goldzieher and Sherman[83] have found hypertrophy of the musculature of the suprarenal vein in hypertension and in certain cases of renal disease without high blood pressure the significance of this finding is not clear

3 Neubauer[84] found that hyperglycemia is a common accompaniment of arterial hypertension In view of the well-known fact that the injection of epinephrin elevates the blood sugar by mobilizing glycogen this finding has been interpreted in favor of the epinephrin theory of hypertension

tumor with hypertension and added another with necropsy proof and a second in which there was no necropsy but the diagnosis seemed beyond doubt (clinical picture now known as Cushing's syndrome)

That the hypertension and the cortical tumor are not merely coincidental findings having no connection with one another is immediately *indicated* by the *occurrence* of cortical tumors or hyperplasia and hypertension in young children in whom hypertension other than that due to glomerulonephritis or urinary obstruction is a great rarity. Thus Hoag[99] reported *an instance of cortical* tumor in a child aged *four years* whose blood pressure was 160/100 mm and Bullock and Sequeira[22] a similar case in a child aged eleven years. Neither had glomerulonephritis nor disease of the urinary passages. The final proof that the suprarenal tumor is responsible for the hypertension is afforded by the return of the blood pressure to normal following the removal of the growth. This was first observed in 2 cases by Volhard[100] and has since been reported in a considerable number of *instances (page 930)*

Since hypertension due to tumor of the adrenal cortex disappears after removal of the growth it presumably is due to hypersecretion of one or more of the cortical steroids. The hypertension does not result from suppression by the tumor of any antipressor cortical secretion because it occurs while the contralateral normal adrenal is functioning

2 Vaquez[77] long ago observed that diffuse hyperplasia and circumscribed adenoma formation are common in the adrenal cortex in hypertensive patients. Similar observations have since been made by Aubertin and Ambard[101] Philpot[102] Oppenheimer and Fishberg[97] Rhinehart[103] *et al* and Russi[104] *et al*. In essential hypertension Rhinehart found almost regularly a grossly thickened and nodular cortex with microscopic hyperplasia of the adrenal cords which were usually well filled with lipoid droplets; the mean weight of the adrenal in essential hypertension was 4.2 grams more than in their controls. Fisher and Hewer[105] likewise observed increased lipid content of the adrenal cortex in hypertensives. Contrariwise Dempsey[106] and Commons and Callaway[107] found no correlation between hypertension and hyperplasia and adenoma formation in the adrenal cortex. Further investigation is needed to reconcile these important differences. In the writer's experience grossly obvious adenomas are more common in patients with severe hypertension and the average size of the cortex is greater in the latter. Rather[108] found the adrenals enlarged in rats with experimental hypertension

3 Hypertension may be produced in both man and the experimental animal by administration of some of the cortical steroids. This was first accomplished with desoxycorticosterone acetate (DOCA) by Loeb[109] and his associates. They observed the development of hypertension in patients with Addison's disease as a result of treatment with DOCA. Nowadays most patients with Addison's disease receiving DOCA have hypertension at one time or another; the elevation in pressure develops gradually, is documented in both the systolic and diastolic levels and disappears with discontinuation of the drug. The observations of De Gennes[110] *et al* show that if an Addisonian is given enough DOCA he may develop a picture resembling spontaneous malignant hypertension. In 3 young men without

mary arterial pressure, and most often tachycardia. Each of these findings contrasts with that in essential hypertension. It appears that the pressor effect of epinephrin in man *in these doses*, contrary to what was long generally thought, is due to increased cardiac output, and that peripheral resistance falls as a result of predominant vasodilatation. This is, of course, diametrically the opposite of the mechanism of elevation of blood pressure in essential hypertension which is due to widespread peripheral vasoconstriction without change in cardiac output.

(*b*) Piperoxane hydrochloride and other adrenolytic agents depress the blood pressure in hypertension due to pheochromocytoma but not to essential hypertension (page 935).

In the light of these findings there is no support for the theory that elevation in blood pressure in essential hypertension is a manifestation of hyperepinephrinemia.

Nor-l-pinephrin.—Nor epinephrin (arterenol) differs from epinephrin only in the attachment of a methyl group to the nitrogen atom in the latter. Both catechols are present in the normal adrenal medulla and, in widely varying proportions, in pheochromocytoma (Goldenberg *et al.*). It was mentioned above that Goldenberg's studies have shown that while the hypertension produced by epinephrin is due to increased cardiac output that of arterenol results from arteriolar constriction.* This brings up the possibility that essential hypertension may be due to increased secretion of nor-epinephrin. However, there is no convincing evidence for this view and much against it. Goldenberg found in humans that piperoxan also depresses hypertension due to arterenol.

Recently Goldenberg and his associates have suggested that secretion of epinephrin or arterenol may initiate hypertension which is then perpetuated by other mechanisms. They base this theory on observations indicating that continuous hypertension may occur in pheochromocytoma *in which there is only intermittent circulation of the adrenergic agent*. They found that hypertension persisted in 7 of 12 patients with pheochromocytoma for varying periods up to 11 months after the tumor had been resected. Interesting as is the possibility that hypertension may be initiated by adrenergic discharge and then perpetuated by other mechanisms, further evidence is required before it can be regarded as probable.

The Adrenal Cortex.—There is evidence which shows beyond cavil that disease of the suprarenal cortex can produce hypertension and calls for investigation of the possibility that it may be concerned in the pathogenesis of essential hypertension. Some of the evidence for and against this possibility may be outlined seriatim.

1. That disease of the suprarenal cortex can produce hypertension is shown by cases of cortical tumor or hyperplasia accompanied by hypertension. Above were mentioned the two such cases observed by Neusser; another had been published previously by Fraenkel.[96] In 1924 Oppenheimer and the writer[97] collected from the literature 13 cases of suprarenal

* This general statement refers to the findings in man with doses of the catechol that produce the degree of hypertension mentioned in the text. On intravenous or intra-arterial infusion into anesthetized dogs Wakim and Essex[98] found that identical doses of *l*-epinephrin and *l* nor epinephrin have the same effect on the arterial pressure, heart rate and blood flow.

vanced lymphosarcoma only after two weeks when general anasarca with gain in weight of over 20 pounds had developed did a moderate hypertension of 160/105 mm appear which vanished as did the edema when the hormone was discontinued. Selye's[122] diversified experiments on various mammals and the observations of Perera[1?] on patients indicate the great difficulty in producing hypertension by administration of DOCA to normals. Quite the contrary is true as indicated by the above mentioned observations on patients with Addison's disease or insufficiency or absence of the adrenals. Swingle[123] *et al* showed that DOCA raises the blood pressure more readily in the adrenalectomized than in the intact animal. Similarly Knowlton[12?] and her coworkers found in rats with experimental nephritis that cortisone produces far more hypertension in adrenalectomized animals. It is said that potent whole cortical extract contrary to DOCA is incapable of producing hypertension in normal or adrenalectomized animals or in Addison's disease (Grollman[1?] *et al*, Soffer[1?]). A few observations by Perera and Pines[1?] indicate the possibility that simultaneous injection of an adrenal cortical extract blocks the pressor effect of DOCA which they observed in hypertensive patients. Observations such as these are in accord with Soffer's conception that individual cortical steroids counterbalance one another in their effect on the blood pressure. Hypertension originating in or mediated by the adrenal cortex would then be a result of dysequilibrium between different corticoids.

(c) There is strong evidence that *DOCA and presumably the naturally occurring corticoids which raise blood pressure produce hypertension at least largely through the intermediacy of alterations in the sodium economy.* Selye[1?] showed that the administration of sodium salts enormously increases the ability of DOCA to produce hypertension. This has been confirmed by Knowlton[129] and her associates and others. Contrariwise DOCA does not produce hypertension if sodium intake is sufficiently reduced. Thus Braun-Menendez and Prado[130] found that the implantation of 40 mg of DOCA does not elicit hypertension in rats on a sodium poor diet and tap water; addition of 4 per cent of sodium chloride to the diet produces hypertension in animals given the same amount of DOCA. In Knowlton's experiments on rats with Masugi nephritis DOCA produced hypertension only with adequate sodium intake. Braun-Menendez finds that when DOCA and sodium salts produce hypertension in rats there are always renal lesions and increase in extracellular fluid volume and believes that both these factors may be concerned in the causation of the hypertension. However it seems unlikely that renal lesions play a primary pathogenetic role (see below). Much still remains to be learned regarding the nature of the interplay between DOCA and sodium salts in the production of hypertension but it seems likely that an important factor is the retention of sodium that the hormone produces through favoring tubular reabsorption.

The additional possibility exists however that other mechanisms than those operating through sodium retention may also be concerned in DOCA hypertension. In the original observations of Perera[111] and his associates on DOCA hypertension in the Addisonian and normal man they were unable to correlate the rise in pressure with sodium retention or increase in blood volume.

adrenal disease Perera[111] *et al* were able to produce elevation of blood pressure by administration of 10 mg daily of DOCA plus sodium chloride

Administration of DOCA to the dog in large doses over a protracted period produces modest hypertension (Kuhlman[112] *et al*) However this animal is very resistant to the induction of hypertension by DOCA Visscher[113] did not produce hypertension in dogs by the daily administration for a month of 25 mg of DOCA and 75 to 125 gm of sodium chloride Masson[114] and his associates found that even after uninephrectomy DOCA has little effect on the blood pressure of dogs The steroid much more readily causes high blood pressure in the rat (Grollman[115] *et al*, Selye and Hall[116]) which has become the favorite animal for the study of this type of hypertension Even more susceptible is the chick in which Selye[117] has found that even small doses of DOCA produce high blood pressure

Cortisone and ACTH have little effect on the blood pressure in the vast majority of patients with rheumatoid arthritis and other conditions including the nephrotic syndrome for which these hormones are used But occasionally especially with large doses administration of either of the hormones results in definite rise in blood pressure which disappears with withdrawal In Candeo's patient whom the writer also observed injection of ACTH for scleroderma was followed by the typical syndrome of malignant hypertension necropsy revealed renal vascular lesions resembling those of periarteritis nodosa While Perera[118] observed slight decreases in the blood pressure with cortisone Corcoran[119] *et al* found no significant change in arterial tension in 2 patients with essential hypertension given cortisone for two to five weeks and 2 others given ACTH for the same period

Selye[120] produced hypertension in rats with injections of 11-desoxocortisone (Reichstein's compound S) but Masson[121] *et al* were unable to obtain the same result with pellet implants The production of hypertension by desoxocortisone is important because this steroid occurs normally in the adrenal cortex while desoxycorticosterone though demonstrated by Reichstein in the normal cortex apparently occurs only in minute quantities

How DOCA produces hypertension has been the object of much study—largely in the hope of elucidating the role of corticoids in hypertensive diseases—but the question has not yet been answered The following are some of the relevant findings

(*a*) DOCA does not have a directly pressor action like for example arterenol the pressure rises only after days indicating that the elevation results from changes in the organism wrought by the steroid and not directly from the circulation of the latter The steroid does not increase the sensitivity of the vessels to such pressor agents as epinephrin renin or angiotonin (Masson[114] *et al*)

(*b*) It is far more difficult to produce hypertension with DOCA in normals than in individuals with Addison's disease While almost every Addisonian getting therapeutic doses of DOCA has periods of hypertension large amounts of DOCA must be given for a long time to persons with intact adrenals to produce definite hypertension When DOCA first became available the writer administered 15 mg daily to a patient with far ad

not by salt alone These observations on adrenalectomized hypertensive animals and patients contain no evidence that hyperfunction of the adrenal cortex is the *primum movens* in essential or experimental hypertension The fall in pressure following bilateral adrenalectomy suggests no more than that some cortisone or DOCA like factor is essential for the maintenance of an elevated blood pressure but affords no indication of the cause of the latter Indeed the experiments of Turner and Grollman[108] indicate that hypertension can be maintained without even the homeostatic participation of adrenal cortical secretion in totally nephrectomized and adrenalectomized dogs maintained for as long as 40 days by intermittent peritoneal lavage hypertension equal to that of dogs which were only nephrectomized developed without administration of any hormone

5 Victor[140] described hypertension in dogs following ligation of arteries and veins at the hilus of one adrenal Goldblatt[141] was unable to confirm the result

6 Attempts have been made to obtain information regarding the role of the adrenal cortex in hypertensive diseases by determinations of corticoids in blood and urine The 17 keto steroid content of the urine—using the Zimmerman reaction and including steroid derivatives of adrenal and testicular origin—is normal in most patients with essential hypertension (Bruger[142] *et al*) Raab[143] reported that in essential hypertension the resting level of what he regards as adrenocortical compounds in the blood is normal but contrary to healthy controls is elevated briefly after exercise He found no relation between the level of adrenocortical compounds in the blood and the height of the blood pressure in essential hypertension Raab found an increase in adrenocortical compounds in the blood in renal hypertension Daughaday[144] *et al* and Tobian[145] found normal values for formaldehydogenic corticoids in the urine in essential hypertension but Corcoran[146] and associates observed an increase in 20 of 46 patients with essential hypertension in the benign or malignant phases and in 9 of 10 in whom there were 4 or more observations They conclude that the variability of corticoduria is increased in hypertension Dobriner[147] and associates found Δ^9-etiocholenolone in the urine of 3 of 6 women with essential hypertension As yet the study of corticoids in blood and urine has thrown no light on the role of the adrenals in hypertensive diseases It would however seem to merit further study

7 Study of the sodium economy in essential hypertension (page 726) has afforded no evidence that the elevation in blood pressure results from adrenal dysfunction

8 The only form of hypertension demonstrably originating in the adrenal cortex that of the Cushing syndrome is accompanied by a variety of other manifestations of cortical hyperactivity (page 928) None of these is present consistently in essential hypertension

9 Mirsky[148] and his associates studied the insulin tolerance of 21 hypertensive subjects They found that the rate at which blood sugar decreases after a standard dose of insulin is the same as in normals but the rate of restoration from the hypoglycemic state is delayed The normal rate of fall of the blood sugar indicates that there is no increase in circulating anti insulin agents and consequently that the activity of the adrenal cortex or anterior pituitary is not augmented

(*d*) The possibility that DOCA produces hypertension through the intermediacy of the kidney, perhaps by activating the renin angiotonin mechanism, has repeatedly been considered. Selye[13] showed that in rats, especially if potentiated by unilateral nephrectomy and high sodium intake, administration of DOCA produces arterial and renal lesions. Friedman and Friedman[133] noted that the hypertension caused in rats by DOCA is paralleled by hypertrophy of the kidney. In mice injection of adrenotropic hormone is followed by hypertrophy of the juxtaglomerular apparatus, but there is no evidence of hypertension in the weight of the heart (Dougherty[134]). Zweifach and Shorr[135] detected no indications that DOCA hypertension in rats is due to VEM. Braun-Menendez showed that when administration of DOCA and sodium salts to rats produces hypertension there are both renal lesions and increase in extracellular fluid volume; he concludes that both the renal lesions and the expansion of the extracellular fluid may be concerned in the genesis of the hypertension. However, it appears that the kidneys are not essential for the pathogenesis of hypertension resulting from DOCA, for Hall and Hall[136] have shown that the blood pressure of rats with such hypertension continues to rise after bilateral nephrectomy; no such degree of hypertension developed in their controls which were nephrectomized without administration of DOCA. The arteriolar and renal lesions which Selye first produced in rats with DOCA and sodium salts may well be the result of the hypertension; they appear similar to or identical with those seen in the contralateral kidney of rats with severe hypertension due to unilateral constriction of the renal artery. Such renal lesions may then in turn produce hypertension; they perhaps explain the finding of Friedman and Friedman that when DOCA hypertension has been present for several weeks it may persist despite cessation of the hormone.

The available evidence would seem to indicate that DOCA produces hypertension through the intermediacy of sodium retention by favoring tubular reabsorption of the cation. According to this view, DOCA hypertension is fundamentally similar to the hypertension produced in rabbits by drinking salt solution (page 724). Whether or not the hypertension resulting from administration of DOCA to a suitably prepared animal or in Addisonian has any relation to human essential hypertension remains to be determined.

4. In his pioneer experiments Goldblatt[138] showed that while the elimination of both adrenal medullas does not interfere with the production of hypertension by constriction of the renal artery in dogs, the blood pressure falls to normal after bilateral adrenalectomy. However, the hypertension can be restored by a potent cortical extract, dehydrocorticosterone acetate or DOCA (Page and Lewis[139]). Similarly, relatively small doses of cortisone suffice to maintain blood pressure above normal in patients with essential hypertension who have been treated by total adrenalectomy (page 923). Doses of cortical extract, DOCA or cortisone equal to the amount that maintains hypertension in a Goldblatt dog or adrenalectomized patient will not raise the blood pressure in normals. Perera[140] observed that in a hypertensive patient who developed Addison's disease the hypertension disappeared during hypoadrenalism but was restored by steroids, though

function of the adrenal cortex even in the cases in which Cushing's syndrome is due to pituitary disease there seems every reason to believe that the hypertension and other clinical manifestations are produced indirectly through stimulation of the adrenal cortex. However in his pioneer studies Cushing concluded without adducing direct evidence that the hypertension of his syndrome is due to an excess of neurohypophyseal secretion. He found that patients with chromophobe adenoma which compresses the posterior lobe always have subnormal blood pressure an observation compatible with his conception that the hypertension of basophilic adenoma results from hyperactivity of the posterior lobe. As a corollary of his theory that the hypertension of the Cushing syndrome results from basophilic hypersecretion Cushing advanced the hypothesis—for it was no more—that the immediate mechanism of essential hypertension is secretion of an excess of the pressor principle of the posterior lobe. This hypothesis was based largely on his finding that in essential hypertension and eclampsia there is massive basophilic infiltration of the pars nervosa of the hypophysis though somewhat less in degree than in the syndrome of basophilic adenoma. Cushing also observed an increase in the hyaline substance within the gland which he considered the secretory product. He called attention to observation by others indicating an increase in the basophiles of the adenohypophysis in renal and other varieties of hypertension. With little supporting evidence Cushing regarded the extent of basophilic infiltration of the neurohypophysis as a measure of posterior lobe activity. However even the correlation of augmented basophilic invasion of the posterior lobe with hypertension has not been confirmed. While Ahlstrom[188] Lewy and Zimmerman[15] and others found basophilic infiltration of the posterior lobe more common in hypertensives even these investigators observed many patients with pronounced hypertension but little basophilia and contrariwise other individuals with marked basophilic infiltration of the neurohypophysis but normal blood pressure. In a careful and well-controlled study of the pituitary glands from 70 persons with essential hypertension 33 with evidences of antecedent hypertension and 108 with normal blood pressure Sparks[9] found no greater degree of basophilic infiltration of the pars nervosa in essential hypertension than in controls of similar age.

Attempts to demonstrate an excess of pitressin in the cerebrospinal fluid or blood of patients with essential hypertension or with the Cushing syndrome have failed (page 702). On the other hand the observations of Birchall *et al*[160] on the renal handling of injected hypertonic saline showed that pitressin is not lacking in the blood of patients with essential hypertension or the Cushing syndrome.

The possibility that excessive secretion of ACTH participates in essential hypertension merits consideration. In rare cases—the writer has seen two—administration of ACTH to normotensives leads to malignant hypertension. Appel *et al*[161] observed hypertension in 3 of 17 normotensive soldiers to whom they gave a daily intravenous injection of 20 mg of ACTH for thirty one consecutive days. However there is no good evidence that hypersecretion of ACTH is primarily concerned in the pathogenesis of essential hypertension (*cf* also Selye's stress theory page 741). Since ACTH stimulates secretion of multiple if not all the hormones of the

10. By studying the sodium and chloride concentrations in the sweat Davies and Clark[149] found evidence of hyperactivity of the salt retaining hormone of the adrenal cortex in not more than 20 per cent of cases of essential hypertension; these perhaps correspond to the patients with essential hypertension in whom Schroeder[150] and these investigators pointed out the existence of a syndrome—including hypertension, obesity and menstrual irregularities—simulating adrenal cortical hyperfunction. However, Davies and Clarke's observations on the sweat revealed no evidences of adrenal cortical hyperfunction in the large majority of hypertensives. The observations of Eisenberg *et al*[151] on the sodium concentration in the sweat also revealed no evidence of increase in the level of electrolyte-influencing adrenal cortical steroids.

Summary.—That adrenal cortical activity can produce hypertension is proved by the Cushing syndrome. Also demonstrated is that neither clinical nor experimental renal hypertension is maintained in the absence of the adrenal cortex or replacement therapy. But *there is no convincing evidence that essential hypertension originates in the adrenal cortex or that the latter plays other than a secondary and homeostatic role in the disease*.

THE HYPOPHYSIS

The classical disturbance of pituitary secretion, acromegaly, presents no characteristic abnormality in blood pressure. Nevertheless, in view of the long known pressor property of extracts of the posterior lobe it is not surprising that the possibility that the hypophysis might be concerned in the genesis of high blood pressure has been discussed repeatedly. Some of the earlier observations were mentioned in the first two editions of this book but none of them carried any conviction and it was not until the description of the Cushing syndrome that the pituitary factor in hypertension was seriously studied.

That hypertension can exist in the absence of pituitary activity has been shown experimentally. In Goldblatt dogs Page and Sweet[15] found that while hypophysectomy produces a fall in pressure, tighter constriction of the renal arteries causes the pressure to rise further. Goldblatt[153] *et al* showed that complete hypophysectomy does not prevent the development of hypertension when the renal arteries are constricted in the dog or permanently lower the pressure in such a dog. Anderson[154] and his associates showed that when the blood pressure falls following hypophysectomy in rats with renal hypertension the elevation is restored by ACTH. Braun Menendez[1] long ago found that hypophysectomy produces a fall in blood pressure in normal dogs; since he showed that removal of the posterior lobe does not affect the blood pressure, the fall is due to loss of adenohypophyseal function, perhaps the result of elimination of stimulation of the adrenal cortex by ACTH.

The first indication that disease of the hypophysis might produce marked and protracted hypertension was embodied in the classic description by Cushing[116] of the syndrome now known by his name (page 928). Hypertension is a cardinal feature of this syndrome. The data now available indicate that the hypertension of the Cushing syndrome is a manifestation of hyper

completely alleviated. The concept of menopausal hypertension probably owes a large part of its wide acceptance to the circumstance that essential hypertension is often asymptomatic for many years and may be detected only when the woman comes to the physician because of menopausal symptoms which have no connection with the hypertension; the results of treatment with estrogen often differentiate the two independent conditions. As yet there is no good evidence that ovarian insufficiency plays a part in the pathogenesis of essential hypertension.

Myoma Heart.—Another group of cases of essential hypertension which may be considered at this point is that occasionally found in association with fibromyoma of the uterus and other diseases of the female reproductive organs. Cardiac disturbances were described in patients with fibromyoma by Hofmeier[168] in 1880. Of 901 *cases* of uterine fibroid collected from the literature by Crossen[169] 38 per cent had cardiac manifestations, an incidence too high to be merely accidental. *The term* "myoma heart" has been applied, particularly in the German literature, to cardiac abnormalities *found* in association with fibromyoma. It would seem, however, that myoma heart is not a unitary concept. In some instances the enlargement of the heart with such subjective disturbances as dyspnea and palpitation is the result of the anemia produced by long-continued uterine bleeding. Not rarely, associated obesity produces dyspnea and other symptoms. In other cases, however, there is arterial hypertension which may cause cardiac symptoms. The nature of the relation between fibroids and arterial hypertension, if any, is not clear. Polak *et al*[170] found that fibroids have no effect on the blood pressure in young women; when hypertension was associated with fibroids in their cases it was always in older women. Mueller[171] believed that fibromyoma not uncommonly results in arterial hypertension. He stated that he had seen several cases of fibromyoma with hypertension in which operative removal of the tumor was followed by the return of the blood pressure to normal, though this did not occur after radiation treatment. The same sequence seems to have happened in a few of Everett's[172] patients, though I do not recall having observed relief of hypertension which could be unequivocally attributed to removal of pelvic masses. Fetter and Schnabel[173] observed the same incidence of hypertension in women with fibroids as in others under the age of forty years, but above this age hypertension was more common in the women with fibroids. Strassmann and Philipp[174] found a higher incidence of hypertension in 500 *women* with fibroids than in 500 others of the same age groups. In an exact statistical investigation Alvarez and Zimmermann[175] found that women with fibroid disease have higher average blood pressures than normal women. In fact, they found that various abnormalities of the female reproductive organs—masculine distribution of body hair, sexual anesthesia, fibroids of the uterus and pelvic conditions requiring ovariectomy or hysterectomy—are associated with high average pressure. Alvarez and Zimmermann believe that in these cases elevation of blood pressure occurs only in those with an inherited tendency to hypertensive disease, which is brought on prematurely by the abnormality of the reproductive organs. Everett and Scott[176] also observed a higher incidence of hypertension in women with fibroids or uterine prolapse than in controls.

adrenal cortex, the absence of other manifestations of the Cushing syndrome militates against the existence of ACTH excess in essential hypertension

That the insulin tolerance of hypertensive patients affords no indication of increased activity of the anterior pituitary was mentioned on page 711

In pursuance of his extensive experiments on hypothalamic function Heinbecker[162] has evolved a hypothesis of the pathogenesis of essential hypertension involving a pituitary imbalance He believes that nervous influences from the frontal lobes depress the supraoptic and paraventricular nuclei of the hypothalamus This depression causes decreased neurohypophyseal secretion in consequence of which the eosinophiles of the adenohypophysis are stimulated to increase their output of ACTH More evidence is needed before these conceptions can be regarded as other than hypothetical in their relation to essential hypertension

In brief *there does not appear to be evidence that the pituitary plays other than a homeostatic role in the pathogenesis of essential hypertension*

THE GONADS

Menopausal Hypertension —The widely accepted concept of menopausal hypertension originated with Huchard[163] who observed that hypertension often appears at the time of the menopause he spoke of hypertension arterielle de la menopause Such hypertension may accompany or follow either the natural menopause or that produced by either operative or roentgen castration However well marked hypertension occurs in only a comparatively small proportion of women at or soon after the menopause Lehfeldt[164] noted it in only 16 of 111 women passing through either a natural or an artificial menopause and in several of these it may have been due to other causes He found that abnormally great fluctuations in blood pressure are a more frequent climacteric manifestation than is true hypertension such fluctuations exceeding 15 mm in the systolic pressure were present in 23 per cent of climacteric women In 200 women desiring relief of menopausal symptoms 179 of whom had been surgically castrated Taylor[165] *et al* found no greater incidence of hypertension than in the general population only 6 developed high blood pressure following the menopause and 5 of these were over forty years of age

It would thus appear that in a strict sense *there is no such entity as menopausal hypertension* the incidence of hypertension at or shortly after the natural or induced menopause is hardly greater than in women of the same age without ovarian failure It is true that on rare occasions one encounters an abrupt rise in blood pressure in the months following surgical or roentgen castration but a similar rise is sometimes seen in other women and in males The usually modest fluctuations in blood pressure that may accompany the vasomotor phenomena of the climacteric are by no means always indicative of future hypertension Another evidence that hypertension in climacteric women is not due to elimination of ovarian activity is the failure of estrogens to lower the blood pressure Ayman[166] and Mayer[167] and his associates saw little effect on hypertension from the administration of estrogen my experience has been the same even when the vasomotor phenomena and other symptoms of the menopause are

however that hyperthyroidism may intensify an inherited tendency to essential hypertension perhaps through the augmented cardiac output and blood volume In favor of such a conception are the observations of Bøgard[188] that in some (by no means all) patients with both thyrotoxicosis and essential hypertension subtotal thyroidectomy may be followed by reduction of the elevated diastolic pressure I have made similar observations though in only a minority of the cases

Hypothyroidism —In most instances of myxedema the blood pressure is rather low However there are cases of hypothyroidism which are accompanied by marked hypertension The author[189] published such a case

A previously healthy boy aged sixteen years rather suddenly started to gain weight until his obesity became extreme Development of the primary and secondary sexual characteristics was greatly retarded His blood pressure rose to 175/135 mm He died of cerebral hemorrhage at the age of twenty-one years At necropsy very extensive atrophy of the thyroid gland was found The pituitary and suprarenal glands presented no structural abnormalities the testes showed only diminished spermatogenesis There was generalized arteriosclerosis and slight arteriolosclerotic changes in the kidneys but no glomerulonephritis

I have also seen another instance of marked hypertension in a myxedematous woman aged thirty two years though it was but little lowered when she took large doses of thyroid which relieved her other symptoms Moreover a survey of the reported necropsies in myxedema (see the paper just cited) reveals that cardiac hypertrophy granular kidneys and severe arteriosclerosis are not uncommonly present Whether the association of myxedema with essential hypertension is purely coincidental or whether the hypothyroidism elicits the hypertension through the extensive atherosclerosis always present in even youthful myxedematous subjects or some other mechanism remains to be determined There have been a number of reports (*cf* Menof[190]) that administration of thyroid extract lowers the blood pressure in some patients with essential hypertension I have seen no evidence of this While there is often some reduction in blood pressure when obese individuals with hypertension take thyroid extract in the belief that it helps in weight reduction the lowering in pressure is probably correlated with the loss of weight due to dietary restriction most of the individuals in question have no hypothyroidism and similar reduction in blood pressure is observed without the administration of thyroid

The Liver and Pancreas —The functions of the liver and the pancreas in hypertension are discussed below there is no evidence that either is concerned in the pathogenesis of the disease

Summary That hormonal disturbances *per se* can produce chronic hypertension having the characteristics of essential hypertension is shown by the primary or secondary hyperfunction of the adrenal cortex that results in Cushing's syndrome in pheochromocytoma and probably by the hypertensive toxemia of pregnancy and rare hormonal tumors of the testicle There is also evidence that a modicum of adrenal cortical function or adequate replacement therapy is necessary for the maintenance of any form of hypertension Nevertheless *there is as yet no proof that essential hypertension results from an endocrine disturbance*

of similar age. Since the hypertension occurred more often in women in whom the intravenous pyelogram disclosed dilatation of the ureters they believe that interference with urinary flow over long periods may be concerned in the genesis of the elevation in pressure.

The Testis. — There is no indication that the testis is concerned in the pathogenesis of essential hypertension. While Steinach,[177] Walker[178] and others reported that testosterone propionate may lower the blood pressure of hypertensives, this was not confirmed by Green[179] and Lattimer.[180] I have not noted any effect of testosterone on elevated arterial pressure in men being treated for the "male climacteric." With the Hamilton manometer, Blackman[181] and his associates found no change in the arterial pressure of puppies from testosterone. Adams[182] observed hypertension in a man of twenty-two years with a chorionepithelioma of the testis whose urine contained large amounts of gonadotropic hormone and cites other malignant testicular tumors with positive Friedman tests in which there was hypertension. Hypertension in such testicular tumors may be related to the high blood pressure of the toxemia of pregnancy or the Cushing syndrome but throws no light on the pathogenesis of essential hypertension.

There would seem to be no evidence that the gonads are concerned in the causation of essential hypertension. Nor does gonadectomy in either sex have any effect on experimental renal hypertension in the dog (Goldblatt).[183]

THE THYROID

Most patients with essential hypertension have no abnormality in oxygen consumption (*cf.* however page 818). Thyroidectomy does not interfere with experimental renal hypertension (Goldblatt).[183] Nor do clinical observations, as will be seen in the following, afford any evidence that the thyroid is concerned in the pathogenesis of essential hypertension.

Hyperthyroidism. — The large majority of individuals with Graves' disease, particularly the younger ones, do not have true hypertension. As is clearly seen from the tables of Plummer,[184] the systolic pressure in thyrotoxicosis is usually moderately or even considerably elevated but the diastolic pressure is normal or more often somewhat low. Apart from these expressions of the alterations in circulatory dynamics due to hyperthyroidism, there is a group of cases in middle life studied especially by Bois and Shapiro[185] who have both true diastolic hypertension and thyrotoxicosis. It is not uncommon for patients with long standing thyrotoxicosis but no diastolic hypertension at first to develop diastolic hypertension when he or more often she reaches middle life. Hurxthal[186] found no evidence that hyperthyroidism leads to essential hypertension but I have a decided impression that essential hypertension is more common in middle-aged individuals who suffer or previously suffered from Graves' disease than in the general population (see also p. 819). Parkinson and Hoyle[187] have also observed the frequent concomitance of hypertension and hyperthyroidism in individuals over the age of forty years. However, the hypertension in such individuals cannot be attributed directly to the thyrotoxicosis for much more severe Graves' disease in the young, even though present for years, does not produce elevation of the diastolic pressure. It seems likely

many women who consume comparatively little during the regular meal but while cooking in the kitchen are continually taking small bites to eat which mount up considerably at the end of the day. The amount of nutritive material ingested by heavy beer or wine drinkers is also great even though they do not take an excess of solid food. This is a phenomenon which however has scarcely been seen of late in this country for few have drunk beer in quantities comparable to those which were formerly often taken in Munich. On restriction of the diet particularly in obese persons it is not uncommon to see a moderate drop in blood pressure.

On the other hand there are many persons who have partaken of a seemingly excessive dietary throughout a long life and have normal blood pressures. This is even the case in many instances in which great obesity has resulted from eating too much. And there are many individuals with hypertension who have always eaten sparingly. From these facts it seems clear that superalimentation in itself does not cause hypertension. But it seems a likely inference from the effects of spontaneous and therapeutic undernutrition on hypertensives that overeating may accelerate the appearance of high blood pressure in the prehypertensive stage of essential hypertension or accentuate hypertension already present.

There is a widespread popular belief also held by such distinguished physicians of a former generation as Huchard and with reservations Allbutt that excessive ingestion of meat is particularly potent in elevating the blood pressure. However there seems to be little or no evidence for this opinion. It will be pointed out below that the evidence that a high protein regimen causes essential hypertension is not convincing.

Obesity in relation to hypertension is considered on page 721.

Protein Metabolism.—Older views of the condition now known as essential hypertension regarded it as the result of primary disease of the kidney, the hypertension being a consequence of the retention of pressor substances. These pressor substances were generally thought to be end products of protein metabolism. This theory is however rendered untenable by the fact that essential hypertension does not start with renal insufficiency and the latter appears in only a decided minority of the cases.

Another theory attributes essential hypertension to the excessive ingestion of protein food. Newburgh[192] and his co-workers found that the feeding of large amounts of protein to rabbits, rats and puppies over a long period of time results in renal lesions and arteriosclerosis. The most prominent lesions seem to have been cloudy swelling, atrophy and dilatation of the tubules, but there were also glomerular and interstitial changes. Similar results were obtained by Polvogt et al.[193] Evans and Risley,[194] Nuzum et al.[195] and Blatherwick and Medlar.[196] In the experiments of the last named investigators and others the animals developed renal insufficiency with nitrogen retention. Moise and Smith[197] and Jackson and Moore[198] found that after the removal of one kidney in the rat a protracted high protein diet results in glomerular, tubular and interstitial lesions in the remaining kidney. It was mentioned on page 558 that Smadel and his associates have found that in the glomerular nephritis produced in rats by the administration of nephrotoxic serum a very high protein diet prevents healing. Newburgh and his associates were also able to produce renal

METABOLIC FACTORS IN THE ETIOLOGY OF ESSENTIAL HYPERTENSION

In recent years, metabolism in essential hypertension has been studied extensively, and there have been advanced various theories of essential hypertension as a metabolic disease. Though critical consideration shows that the results of these investigations have been essentially negative insofar as clearing up the nature of essential hypertension is concerned they have nevertheless served to elicit many facts of theoretical and practical significance.

Food Intake.—Both the laity and some of the profession have long thought that there is a correlation between quantity of food ingested and the blood pressure. This belief is not entirely without foundation. The very exact experiments of Keys and his associates[191] have shown that protracted semistarvation leads to fall in blood pressure in healthy young men. On a daily intake of 1,600 calories with 49 Gm. of protein for six months, at the end of the period their subjects showed a fall in blood pressure from the control level of 106.5/69.9 mm. to 94.7/64.5 mm.; the diminution in blood pressure accompanied a decrease in heart rate to 37 beats per minute and in basal metabolism to minus 39.0 per cent. The blood pressure quickly mounted during rehabilitation from the semistarvation and even rose above the control levels when the subjects ate excessively. Brozek *et al.*[191] cite some very interesting observations during World War II showing that protracted undernutrition results in decrease in blood pressure in both those with previously normal pressure and hypertensives. Especially noteworthy and detailed were the observations during the siege of Leningrad. Accompanying the emaciation of the semistarvation during the siege were a decrease in blood pressure in normotensives, a diminution in the number of hospital admissions for hypertension, and reduction to normal or near normal of the blood pressure in many chronic hypertensives. They cite similar observations by Lups and Francke in Holland in the winter of 1944–45, when the blood pressure fell in 74 per cent of normals and 93 per cent of hypertensives who lost weight. Even more interesting was the remarkable increase in the incidence and severity of hypertension in Leningrad after the siege was lifted and food consumption rose. Compared to the prewar incidence of hypertension, there was a fourfold increase between twenty and thirty-nine years of age, twofold between forty and forty-nine, and threefold over fifty years. Moreover the frequency with which hypertension entered the malignant phase rose above the prewar percentage during this period of renewed availability of food after protracted semistarvation.

Gluttony has long been held a leading cause of hypertension, a view which has been subscribed to by Huchard,[65] Allbutt,[66] Stengel[67] and many others. There can be no doubt that a strikingly large contingent of those with essential hypertension have been gluttons for many years. I have repeatedly been struck by the unusual appetites of relatively young individuals with essential hypertension, particularly before symptoms appear. It should be borne in mind that many who claim to be temperate in food actually eat a great deal. This is especially true in the case of

the blood pressure of 39 patients with long standing essential hypertension did not change.

Studies on dogs with experimental renal hypertension do not indicate that a high protein diet aggravates the high blood pressure. While early observations by Verney and Vogt,[11] Cash and Wood[12] and Maclachlan and Taylor[13] seemed to suggest that feeding large amounts of meat to Goldblatt dogs augmented the hypertension, this has not been borne out by later studies by Phillipsborn *et al.*,[14] Goldblatt *et al.*[15] and Page and Lewis.[16]

In brief, it may be stated that no convincing evidence has as yet been presented that an excess of protein in the diet results in essential hypertension or any other variety of Bright's disease.

Fat and Lipoid Metabolism.—*Obesity.*—It has been seen (page 266) that in health blood pressure tends to rise with increasing weight. In accord with this, obesity is an exceedingly frequent concomitant of essential hypertension. Terry[17] found that 58 per cent of patients at the obesity clinic of the Presbyterian Hospital had hypertension. Robinson[18] and his associates found that obese men have three times more systolic and four times more diastolic hypertension than those who are underweight, while obese women have 6 times more systolic and diastolic hypertension than the lean. The statistical study of United States Army officers by Levy[19] *et al.* revealed a significantly higher incidence of subsequent hypertension in the overweight. Master *et al.*[20] found obesity more than twice as frequent in hypertensive men as in the general population, but in women the difference was very slight. They noted, however, that body weight more than 25 per cent above the standard is hardly more frequent in hypertensives than in normotensives. I have likewise noted that *extremely* obese individuals do not have a notably great incidence of hypertension, especially if one allows for overestimation of the blood pressure because of a very obese arm, and that when it occurs the hypertension rarely enters the malignant phase. Reduction of weight by dietary restriction in obese individuals with hypertension is occasionally accompanied by considerable fall in blood pressure, which usually rises again if the patient gains weight. By no means all patients with essential hypertension are obese; some are very spare. And many individuals with essential hypertension lose a great deal of weight as the disease progresses, despite the fact that the blood pressure is rising. This is especially true if they enter the malignant phase of the disease.

It appears evident that obesity in itself does not cause hypertension, for extremely obese individuals may have low blood pressure, even though there is no evidence of cardiac weakness. Obesity, like hypertension, is often an inherited characteristic, and it seems probable that the same constitutional type is predisposed to both obesity and hypertension, which tend to appear at the same period of life. Likewise overeating tends to increase both weight and apparently blood pressure. The fact that reduction in weight in obese individuals may be accompanied by a reduction in blood pressure—though this is far from always the case—is not an indication that obesity causes hypertension, for dietary restriction may have a similar effect on the blood pressure of thin persons.

lesions by the intravenous injection of certain amino acids which they therefore consider as responsible for the renal damage. Squier and Newburgh[199] claimed that forced protein feeding results in the appearance of red blood corpuscles in the urine of healthy men. Newburgh *et al*.[200] found that a man kept on the enormous protein rations of 338 grams daily developed minimal proteinuria and cylindruria after six weeks which disappeared within ten days after the subject resumed his usual diet. Nuzum and his collaborators believe that the excessive acidity or alkalinity of the urine resulting from different high-protein diets may injure the kidneys. They followed the blood pressure of rabbits kept on a high protein ration for a protracted period and found that hypertension was produced.

On the other hand, Drummond *et al*.,[201] Jackson and Riggs,[202] Anderson,[203] and Osborne[204] *et al*. did not find any notable lesions of the kidney apart from hypertrophy in animals kept for a long time on a high protein diet. It is therefore still an open question whether the large amount of protein in the diet was solely responsible for the lesions of the kidneys in the experiments in which they were produced.

Moreover, the significance of the experiments with high protein feeding for hypertensive disease in man is far from clear. As far as glomerulonephritis is concerned, there can be no doubt that it is of infectious origin, and it has been shown that a meat diet does not predispose to postscarlatinal glomerulonephritis (page 587). And even in those experiments in which renal lesions were produced they bore no resemblance to the arteriolosclerotic renal lesions found in essential hypertension. Nor does clinical experience lend any support to the theory that essential hypertension results from excessive protein intake. Mosenthal[205] and Strouse and Kelman[206] *found that the ingestion of a high protein diet over a considerable* period by patients with hypertension does not elevate the blood pressure and neither does a low-protein diet lower it. That a high protein regimen does not *per se* produce hypertension is well shown by Lieb's[207] report on *Stefansson*, the *Arctic explorer*. He spent eleven and a half years within the Arctic Circle during which he lived on an exclusive meat diet for a number of days totalling nine years, subsisting nine successive months on meat alone. Despite this his blood pressure was 115/55 mm. Thomas[208] found that the Eskimos, whose diet is practically entirely carnivorous, show no increased incidence of hypertension. On the other hand, Iber[209] observed an individual who had been a vegetarian for twelve years but nevertheless had a systolic blood pressure of 220 mm. I have seen several vegetarians with essential hypertension.

Evidence against the view that a high protein intake is concerned in the pathogenesis of essential hypertension is afforded by the results of low protein diets in the disease. It is true that the blood pressure of some patients falls on the Kempner rice diet (20 grams of protein daily), but in others the blood pressure remains high despite protracted *conscientious* adherence to the diet to the point where malnutrition develops, and when lowering of pressure occurs it may be reversed by salt ingestion with no increase in protein intake. Kohan-Kucharik[210] observed that during the siege of Budapest, when animal *proteins were unobtainable for* ten months

very high diastolic pressure notably those with the clinical picture of the malignant phase the serum cholesterol is definitely elevated to between 300 and 400 mg per cent Buerger[223] found no parallelism between the cholesterol content of the blood and the height of the pressure

That hyperlipemia *per se* does not elevate the blood pressure is shown by the normal tension in patients with extreme hyperlipemia due to diabetes biliary obstruction etc There would seem to be no evidence to indicate that abnormalities in lipid metabolism or the concentrations of the lipid fractions in the blood participate in the pathogenesis of essential hypertension Nevertheless the possibility is by no means excluded and merits further investigation the more so because of the likelihood that cholesterol is genetically linked to the cortical steroids and the probably fundamental role of aberrations in cholesterol metabolism in the production of atherosclerosis the lesion which produces most of the tribulations of the patient with essential hypertension Of great interest may be the ultracentrifugal analysis of the serum lipoproteins by Gofman s technique

Carbohydrate Metabolism.—It was mentioned above that hyperglycemia and diminished sugar tolerance are not uncommon in essential hypertension In 23 of 32 hypertensive patients Harris[226] found diminished glucose tolerance in that the peak of the curve exceeded 170 mg per cent or the glucose level did not return to normal within two hours Statistics of the incidence of hypertension in manifest diabetes have not been wholly concordant Adams[230] did not find a high incidence of hypertension in diabetes only one-sixth of his male and a quarter of his female diabetics had a blood pressure above 150 90 mm Joslin[231] found that 19 per cent of diabetics between twenty-one and fifty years and 33 per cent of those over fifty years of age have systolic blood pressures over 150 mm Kramer[232] observed hypertension in 39 per cent of 500 diabetics Major[233] found the systolic blood pressure of elderly diabetic patients higher than that of normal controls In children and young adults with diabetes hypertension is a great rarity the high incidence of hypertension in diabetes being due entirely to its occurrence in diabetics over forty years of age The average systolic blood pressure of Joslin s diabetic patients below the age of forty years was almost exactly equal to the average for healthy individuals but the diabetics over forty years had blood pressures averaging 10 mm and those above fifty years 20 mm above the normal Bell s[234] autopsy statistics show that hypertension is much more common in elderly diabetics than in others of the same age inasmuch as diabetics often enter the hospital because of myocardial infarction and sometimes because of acidotic coma which lower the blood pressure such necropsy observations which take into account cardiac hypertrophy are more dependable than some of the clinical series In my experience hypertension is definitely more common in middle aged and elderly diabetics than in others But how much of this greater incidence of hypertension in diabetes is due to association of diabetes and essential hypertension and how much is due to the operation of the other causes of high blood pressure in diabetics enumerated on p 511 remains to be determined

There does not seem to be evidence that diabetes *per se* plays any role in the production of essential hypertension The fact that hypertension is

Cholesterol Metabolism.—Disturbances in cholesterol metabolism have also been thought to play a part in the causation of essential hypertension. Schmidtmann[70] was able to produce hypertension in rabbits by feeding them cholesterol over a long period. But later the blood pressure fell despite the continuation of the cholesterol feeding and the persistence of hypercholesteremia. She believes that the cholesterol as such does not elevate the blood pressure but serves to sensitize the vessels to pressor substances. Thomas[71] found that while a single injection of cholesterol does not raise the blood pressure, repeated injections cause prolonged hypertension. These results were contradicted by Thoelldte,[72] who was unable to produce hypertension in rabbits by cholesterol feeding over as long a period as four hundred and twenty-three days, though marked arteriosclerosis resulted. Recently Hoffman[73] and his associates observed the development of definite hypertension in 5 of 12 rabbits fed 3 to 20 grams of cholesterol weekly for twelve to one hundred and four weeks. Of the 5 rabbits with hypertension 4 had amyloidosis or paramyloidosis at necropsy; this lesion was not present in the other animal which maintained a mean arterial pressure of between 140 and 205 mm. Hg (direct measurement) for thirty weeks. These observations raise the possibility that when hypertension is produced in rabbits by cholesterol feeding, a renal lesion may be concerned in the pathogenesis.

Some investigators have found that the cholesterol content of the serum is commonly increased in essential hypertension. Westphal[74] observed hypercholesteremia in 71 per cent of his cases of essential hypertension and advanced on tenuous grounds the hypothesis that increased cholesterol content of the plasma sensitizes the arterioles to pressor substances. Wacker and Fahrig[75] also found increased cholesterol content of the blood in 75 per cent of their hypertensive patients; phospholipids and triglycerides were similarly elevated. They found that the proportionate increase of the different lipid fractions in essential hypertension corresponds closely to what they observed during physical exercise in normal controls. For this reason they ascribed the elevation in blood lipids in essential hypertension to increased demand for these substances by the hypertrophied heart and the hypertonic arterioles. Wacker and Fahrig's assumption was that the fatty bodies are mobilized into the blood from the depots in higher concentration as is true of sugar during exercise. Harris[76] also found that total lipids, cholesterol, fatty acids and phosphatides are significantly increased in the serum in essential hypertension; the average serum cholesterol of 125 normotensives was 177 mg. per cent and of 152 hypertensives 237 mg. per cent.

Contrariwise, Page[77] and his associates found that the concentration of cholesterol and the other lipid fractions in the serum is normal in uncomplicated essential hypertension. Only in the malignant phase did they find high lipid values. Likewise Hatch and Kendall[78] found the serum lipid patterns (free and esterified cholesterol, phospholipids and triglycerides) normal in patients with severe hypertension on a normal lipid intake. My experience has also been that the serum lipids are within normal limits in the large majority of patients with essential hypertension, though the average is higher than in normotensives. However, in occasional patients with

In many varieties of experiment Selye[44] has shown that sodium salts aggravate the hypertension and arteriolar and renal lesions produced by desoxycorticosterone acetate In fact there is much in favor of the view that DOCA produces hypertension through the intermediacy of sodium retention (Braun Menendez[32]) and that the hypertension which Grollman demonstrated in nephrectomized dogs (page 334) is at least largely the result of salt and water retention

The above findings are suggestive that sodium retention favors rise in blood pressure But there does not appear to be evidence that sodium retention is primarily concerned in the pathogenesis of human essential hypertension and much that speaks against it

1 In most of the clinical observations on the effects of salt restriction in hypertensive patients the salt intake was not the only variable factor (page 822) Almost always either or both the activities of the patients or the other dietary constituents were also changed and elements of suggestion probably often entered In the studies of Perera and Blood[243] in which an attempt was made to control these other variables the extent of the fall in blood pressure on salt restriction and the rise on salt supplementation was small

2 In the vast majority of patients with uncomplicated essential hypertension the sodium and chloride contents of the plasma are normal While Selye[44] has stated that the *ratio* of sodium to chloride in the plasma is high in essential hypertension this has not been the usual finding in the large material that has become available since the introduction of flame photometry Hypertensive patients without cardiac or renal failure excrete salt loads in at least normal fashion In fact Green *et al*[244] found that following the intravenous injection of 5 per cent sodium chloride solution sodium and water are excreted more rapidly in early hypertensives in direct correlation with the mean blood pressure Farnsworth and Barker[245] had previously found that tubular reabsorption of chloride is *reduced* in hypertensives

3 In hypertensive patients in whom heart failure is treated by salt restriction and mercurial diuresis one often observes maintenance of hypertension despite very low sodium and chloride levels in the plasma A recent patient maintained a blood pressure of more than 210/120 mm despite plasma sodium of 115 mEq and chloride of 80 mEq per liter as contrasted with normal levels for these ions prior to the inauguration of dehydration Likewise in uremic vomiting high blood pressure may persist despite marked fall in plasma sodium and chloride Such cases are common O'Hare and Walker[246] long ago showed that there is no parallelism between the height of the plasma chloride and the blood pressure and the same is true of sodium While such findings tell us nothing of the electrolyte concentrations *in the cells* they do show that there is no relation between the level of the blood pressure and the sodium and chloride content of the extracellular fluid

4 Contrary to the findings in rats Page and Lewis[248] found that salt intake does not affect the arterial pressure in dogs with renal hypertension

5 London and Terry[249] have found that patients with essential hypertension retain more of a sodium chloride load following administration of

rare in young diabetics even though they have had the disease in extremely severe form for years shows that diabetes does not cause hypertension This was well *illustrated by* Mosenthal in a lecture in which he showed charts of diabetics who had had marked hyperglycemia for many years without any *elevation* of blood pressure In fact strikingly low blood pressure is fairly common in diabetics who have been undernourished for a *protracted period* The reduction in blood pressure that occasionally follows successful treatment of complicating diabetes does not indicate *the diabetic* origin of the hypertension for such treatment usually includes limitation of diet and often reduction in weight factors which may lower *the blood* pressure in non-diabetic individuals

In some of the cases of essential hypertension with hyperglycemia or *manifest diabetes* it is possible that pancreatic arteriolosclerosis due to the hypertension is responsible for the disturbance in carbohydrate metabolism However it seems probable that the hereditary predisposition which plays so large a part in both essential hypertension and diabetes is not uncommonly present in the same individual Essential hypertension diabetes mellitus and obesity are a triad which is often found in the same person and it is not uncommon to find one or more of the three in several members of the same family This fact points strongly to a constitutional peculiarity being responsible for both the diabetes and the hypertension

The lack of evidence for the hypothesis that both hypertension and hyperglycemia are the common result of an excess of epinephrin in the blood was pointed out above

Salt Metabolism —The theory that hypertension results from the retention of sodium chloride in the organism was advanced by Ambard and Beaujard[23] who observed that the blood pressure of hypertensive individuals is elevated by the ingestion of salt and lowered by the elimination of salt from the diet In more recent years Allen and Sherrill and others (see Chapter 28) have succeeded in lowering the blood pressure notably in many patients with hypertension by a salt-poor diet Perera and Blood[36] found that the hypertensive patient is more resistant than the normal to the dehydrating effect of salt restriction Also consistent with the theory that abnormalities in the salt economy may be concerned in the pathogenesis of hypertension are the association of salt deficiency with hypotension in Addison's disease and the elevation in blood pressure produced by the administration of salt to such patients In view of the fundamental role of the adrenal cortex in the regulation of sodium exchange the possibility immediately presents itself that any part that sodium may play in the pathogenesis of hypertension may be through the intermediacy or as a result of alterations in cortical function

Experimentally Sapirstein[237] and his associates have produced hypertension in rats by substituting hypertonic sodium chloride solution for their drinking water the rise in blood pressure appeared after they had been drinking the saline for one to four weeks The same was previously accomplished in the chicken by Lenel[238] *et al* Grollman and Harrison[39] showed that rigid salt restriction lowers the blood pressure of hypertensive rats Landis and Abrams[40] found that rats with renal hypertension avoid sodium solutions when given their choice of various solutions for drinking

than incidentally associated noted the association of irregular gout with high arterial pressure He quotes Bruce as having found that the pulse is more tense in irregular than in regular gout Gemmel[58] based on an experience of over 8000 cases states that the blood pressure is elevated in very many gouty subjects Schnither and Richter[59] observed hypertension in 54 per cent of 55 patients with gout In almost all young gouty individuals the blood pressure is normal except for the rise that may occur during a severe paroxysm as a *result of the* pain hypertension generally first appears in the gouty if at all during middle and late life Gout may be present in a severe form for many years with normal or even low blood pressure

There appear to be two forms of hypertension in the gouty

1 Hypertension of renal origin The frequency of renal implication in gout has been known since Garrod's[60] classical studies he found urate deposits in the kidneys of all his patients with tophaceous gout and many of the others Most patients with long-standing gout have proteinuria Serious disturbances in renal excretory function develop in a high proportion of the cases In 22 patients with gout Coombs[61] *et al* found inulin clearance reduced in 9 to between 55 and 75 cc per minute and in 4 to less than 45 cc Eighteen of their 22 patients had hyposthenuria which they regard as the earliest evidence of impairment of renal function in gout The depressed renal function may lead to uremia which is the cause of death in a significant proportion of the gouty At necropsy almost all gouty patients show renal lesions The classical gouty change in the kidney apparently starts with precipitation of urates in the collecting tubules This is followed by necrosis of the epithelium interstitial inflammatory reaction and fibrosis In 2 of Mallory and Brown's[62] 6 cases there was marked pyelonephritis (multiple abscesses in 1) and in another healed pyelonephritis Their findings indicate that the pyelonephritis developed in tubules obstructed by urates the same was true in a case reported by Spitz *et al*[35a] and in one seen by the writer As in all forms of chronic pyelonephritis obstructive lesions of the renal arterioles may develop The kidneys may also be damaged as a result of urinary calculi and ascending infection Ebstein[64] long ago reported instances of gouty kidney in which the joint manifestations were minimal In gouty patients with extensive kidney damage of uratic origin it appears entirely logical to regard hypertension as renal in origin

2 In some gouty patients hypertension appears and persists for several years without evidence of renal damage Such cases would appear to be association of gout and essential hypertension

There is no evidence that gout plays a part in the pathogenesis of essential hypertension

THE LIVER AND ESSENTIAL HYPERTENSION

It has long been known that injection of extracts of various organs has a depressor effect Macdonald[269] and Major[69] observed that liver extracts produce a particularly striking depression of blood pressure in many cases of essential hypertension but Major found little effect on the normal blood

DOCA than without this hormone Soffer[47] *et al* showed that this is the normal response, in contrast to the "diuresis" of salt that follows administration of DOCA in the adrenal cortical hyperfunction of Cushing's syndrome

6 Any theory that would attribute essential hypertension to *renal retention* of sodium or chloride meets the objection that in the Goldblatt dog which certainly has a renal hypertension, the sodium and chloride clearances are normal (page 320) And in man with uncomplicated essential hypertension Brodsky and Graubarth[403] found that under hydropenic conditions renal conservation of sodium chloride may be defective the loss of sodium chloride in the urine exceeding the normal

The evidence available at present thus does not indicate a primary role of derangement in sodium or chloride metabolism in essential hypertension

There have been a few studies of other electrolytes in essential hypertension but they have shed no light on the pathogenesis of the disease

Potassium —In an extensive series of investigations Kylin[50] found the potassium content of the serum slightly elevated and the calcium content diminished in essential hypertension However it seems probable that these findings were due to defects in method in uncomplicated essential hypertension both the potassium and calcium levels in the serum are within normal limits The decrease in blood pressure that De Wesselow and Thomson[54] observed in hypertensive patients given potassium salts was hardly of significant degree Recently Friedman[399] and his associates have observed that a diet deficient in potassium lowers the blood pressure of normal and hypertensive rats and decreases their peripheral vascular reactivity Correspondingly Perera[400] has found that a low potassium diet produced a small but what he regards as statistically significant fall in resting blood pressure in 6 series of observations in 4 patients with essential hypertension More observations along these lines are needed before they can be interpreted

Calcium —Freeman and Farmer[51] stated that the percentage of serum calcium present in diffusible form is somewhat lowered in essential hypertension but I am not aware that this has been confirmed Harris[52] claims that protracted administration of calcium to rabbits produces hypertension this also requires verification In patients Kesson and McCutcheon[53] found no evidence that protracted retention of calcium raises the blood pressure

Magnesium —Weil[256] and Wacker and Fahrig[55] found that the magnesium content of the blood averages slightly above normal in hypertension but the differences do not seem significant and have not been verified

Thiocyanate —Wacker and Fahrig detected no abnormality in the thiocyanate concentration of the blood in hypertension

Bicarbonate phosphate and *sulfate* are within normal limits in uncomplicated essential hypertension

As yet, no abnormalities in the electrolytes of extracellular fluid have been correlated with hypertension

Purine Metabolism —Hypertension is frequently present in gouty subjects The first systematic student of hypertension as such Allbutt[57] though he believed that "regular gout and high pressure are not more

Apart from the transitory hypertension which follows emotion neurogenic hypertension occurs in some diseases of the central nervous system and can be produced experimentally by section of the moderator nerves Hypertension has also been produced by increasing intracranial pressure by electrical stimulation of specific areas of the frontal lobe of the cerebral cortex (Hoff[2] et al) and by damage to the hypothalamus (de Jaegher and Van Bogaert[277] Walter and Pijoan[ ] Heinbecker[182])

Mediation of Neurogenic Hypertension —There seems every reason to believe that neurogenic hypertension is principally or totally mediated through the vasomotor nerves In accord with this general held conception is the finding that experimental forms of neurogenic hypertension are abolished by sympathectomy (see below) In recent years however experimental evidence has been adduced indicating the possibility of renal and humoral mediations of neurogenic hypertension

Renal Mediation of Neurogenic Hypertension —There are forms of experimental renal hypertension which are effectuated through the kidney In these stimulation of the sympathetic nerves to the kidney produces renal vasoconstriction which in turn unleashes the presumably chemical renal pressor mechanism This was accomplished by Kottke[27] et al by electrical stimulation of the nerves to the dog s kidney But even after the hypertension thus produced had been maintained by stimulation for as long as forty five days the blood pressure fell when the stimulation was discontinued Heymans and Bouckaert[290] found that while total sympathectomy abolishes the hypertension due to interruption of the moderator nerves this form of hypertension persists if the sympathectomy is complete except for sparing the nerves to the kidneys Hoff[2] and his associates showed that when hypertension is produced in the cat by electrical stimulation of certain areas of the frontal cortex the volume of the kidneys decreases at the same time that limb volume increases They showed by injection of india ink that the decrease in renal volume accompanied ischemia of the cortex and detected significant amounts of renin in the blood of 3 of their stimulated animals Suggestive as are these experiments it remains to be demonstrated that renal vasoconstriction and the consequent functioning of a renal pressor mechanism plays any part in clinical neurogenic hypertension

Humoral Mediation of Neurogenic Hypertension —Recently Taylor Page and Corcoran[ ] have adduced experimental evidence that the brain can secrete a pressor substance into the blood stream They named the substance *cerebrotonin* By ingenious cross-circulation experiments they have shown that centripetal stimulation of the cut vagus in the neck results in liberation into the circulation from the dog s isolated head of a vasopressor substance which their evidence indicates is secreted by the brain Binet and Burstein[292] also showed that centripetal vagal stimulation in the dog induces liberation into the blood stream of a vasoconstrictor substance The vasopressor action of this cerebral secretion is not inhibited by adrenolytic agents which shows that it is not epinephrine or arterenol Taylor et al find that the cerebral vasopressor substance is strongly inhibited by 1 hydrazinophthalazine and does not induce tachyphylaxis these properties they believe differentiate it from pitressin which Binet and Bur

pressure. These observations in essential hypertension have not been confirmed (4th ed., page 712). There is no convincing evidence that such depressor effects as liver extracts may have are different from those of a wide variety of organ extracts. James *et al.*[70] claimed that the method of preparation of the liver extracts used by Macdonald and Major precluded their containing histamine, choline or peptones, the nonspecific depressor substances present in many organ extracts. Contrariwise, Burnett[1] believes the depressor substance in liver extract is histamine.

Ferritin, the depressor component of Shorr's vasoregulatory system (page 331), and hypertensinogen (page 324) are formed in the liver. However, there is no evidence that any form of hypertension results from excess of the former or deficit of the latter. Haynes and Dexter[7] found the hypertensinogen content of the blood normal in hypertension without renal insufficiency.

Raaschou[273] found that the incidence of hypertension in 102 women with subchronic hepatitis studied at necropsy was lower than in controls. I also have the impression that hypertension is rare in patients with cirrhosis of the liver. The explanation of this finding, which requires substantiation by systematic observations, is not clear. The relevancy of the observation of Haynes and Dexter that the hypertensinogen content of the blood is decreased in some patients with hepatic insufficiency is not demonstrated. Nor is the interpretation clear of Raaschou and Trautner's[40] finding that obstruction of the common bile duct lowers the blood pressure of dogs with experimental renal hypertension.

As yet, there is no substantial evidence that any abnormality of liver function exists in essential hypertension.

THE NERVOUS SYSTEM AND ESSENTIAL HYPERTENSION

In view of the usual pressor response to disturbing emotion, it is not surprising that a nervous pathogenesis has been considered from the earliest studies of what is now known as essential hypertension.* Such a line of thought is rendered all the more appealing by the unequivocal evidence that increased peripheral resistance is the immediate mechanism of the rise in blood pressure, for the vasomotor nerves play a great part in the regulation of the peripheral resistance, especially in determining the partition of blood between different organs. Nevertheless, when it was found that denervation of the kidneys and sympathectomy do not interfere with Goldblatt hypertension (page 321), many deprecated the significance of nervous factors in clinical hypertension. But the studies of the past few years have indicated the need for reappraisal of the role of the nervous system in essential hypertension. And in accord with the *Zeitgeist* an increasing body of critical opinion, not confined to those of primarily psychiatric orientation, regards essential hypertension as a psychosomatic disease.

* Peculiarly enough, Rokitansky,[274] the morphological pathologist *par excellence*, attributed idiopathic cardiac hypertrophy, doubtless predominantly our essential hypertension, to a disturbance of innervation. Laycock,[2] another early student, suggested that Bright's disease results from primary disease of the nervous system.

Bulbar Poliomyelitis —Hypertension may occur in anterior poliomyelitis with bulbar involvement Salus[293] studied 3 patients with ascending spinal paralysis in whom hypertension (200 mm systolic) developed when the process reached the bulb as shown by the development of bulbar speech inability to swallow and paralysis of the hypoglossal nerve One of the 3 cases proved fatal and at necropsy exhibited inflammatory lesions of the central nervous system including the bulb the kidneys were unaffected In the other 2 cases the hypertension persisted for months to disappear as the various paralytic phenomena improved A similar case was published by Mueller and Nordmann[294] the blood pressure reached 200 mm systolic and 140 mm diastolic They found a lesion in the *substantia reticularis grisea* which they believe responsible for the hypertension I have also seen 2 cases of marked hypertension of several weeks duration due to poliomyelitis Inasmuch as the lesions of poliomyelitis cause destruction with loss of function of the involved parts of the nervous system the hypertension in these cases must be due to either damage to a hypothetical vasodilator center or to parts of the nervous system which inhibit the vasomotor center

Transverse Myelitis – In patients with lesions of the upper dorsal or cervical cord hypertension may occur (Thompson and Whitham[295]) usually in conjunction with spinal reflex sweating and other manifestations of sympathetic discharge The blood pressure may rise as high as 240 150 mm and produce violent headache and even convulsions Distention of the bladder commonly and of the rectum exceptionally provoke the pressor crisis (Thompson and Whitham)

Tabes —Paroxysmal hypertension may occur in tabes Bennett and Hyman[296] and others have observed cases in which the paroxysms were so severe that the patient was explored for nonexistent pheochromocytoma It was formerly thought that the paroxysm of hypertension is associated with a gastric crisis and perhaps due to the pain However Bennett and Hyman observed hypertension not associated with gastric crisis or other pain and believe the paroxysm due to some as yet obscure autonomic dysfunction That another disturbance of blood pressure regulation orthostatic hypotension occurs in tabes is well known

Concussion of the Brain —A few instances of paroxysmal and continuous hypertension following cerebral concussion have been described (R[illegible][297]) However hypertension of this causation appears to be very rare and that it ever becomes permanent remains to be demonstrated Raab attributed the hypertension in his 2 cases to injury to the upper medulla oblongata and obtained pharmacologic evidence of hyperirritability of the vasomotor centers

Post Diphtheritic Paralysis —Hypertension has also been observed in this condition (Rosenbaum[298])

Tumor in the Fourth Ventricle —Grimson[299] observed a patient with severe hypertension which was reduced to normal for four years by sympathectomy in whom necropsy revealed a small pedunculated tumor in the fourth ventricle

Hypothalamic Lesions —Heinbecker[300] has described atrophy of the paraventricular hypothalamic nuclei as the basis of some cases of Cushing s

stem hold it to be. Since Page and his associates find that experimental hypertension due to either perinephritis or buffer nerve section is likewise inhibited by 1-hydrazinophthalazine, as is sometimes essential hypertension (page 881), the question of the role of a cerebral humoral mechanism in human hypertension arises. As yet, however, there is no evidence that such is the case.

Neurogenic Hypertension in Disease of the Central Nervous System — *Increased Intracranial Pressure* — An unequivocal example of hypertension due to alteration in the activity of the vasomotor center is that which results from increased intracranial pressure due to brain tumor or other expanding intracranial lesion. The classical experiments of Cushing[283] showed that compression of the medulla leads to immediate rise in the general blood pressure. That the hypertension of increased intracranial pressure emanates from the medulla is proved by Forster's[284] finding that it develops after segregation of the medulla and pons from the structures rostral to them. Anrep and Starling[285] long ago showed experimentally that changes in the blood pressure in the vasomotor center produce the reverse changes in the blood pressure in the rest of the body. The conception that the arterial hypertension of increased intracranial pressure is due to ischemia of the vasomotor center is also supported by the findings of Kety[286] and his associates. Using Kety's nitrous oxide technique for measuring cerebral blood flow, they showed in 13 patients with brain tumor that the rise in cerebrospinal fluid pressure is associated with increased cerebrovascular resistance and, when the pressure exceeds 450 mm. of water, decreased cerebral blood flow. The same was found by Ferris[287] by another method. Basically a similar mechanism, anoxia of the vasomotor center, is apparently responsible for the hypertension that results from asphyxia. Possibly the hypertension produced by anoxia of the vasomotor center is due to local accumulation of waste products, for perfusion of the medulla with an acid fluid produces hypertension (Roberts[288]). It is also probable that anoxia sensitizes the vasomotor center to the carbon dioxide of the blood. The same factors may be concerned in the so-called high pressure stasis (Chapter 26).

Attempts have been made to produce protracted hypertension by other methods of decreasing blood flow through the medulla. Thus by blocking the outflow of the cerebrospinal fluid in dogs by the intracisternal injection of kaolin, Dixon and Heller[289] evoked elevation of blood pressure which lasted for months. Nowak and Walker[290] and Fishback[291] *et al.* induced hypertension in dogs by ligation of the major arteries to the head (carotid, vertebral, spinal). However, Taylor and Page[292] found that hypertension was produced by this method in only 24 per cent of the surviving animals and lasted only seven to fifteen days. By combining ligation of the cephalic arteries with thermal and mechanical stimulation from a tantalum wire in the floor of the fourth ventricle heated by diathermy, Taylor and Page produced hypertension which lasted as long as two to ten months. Since they found that the effects on blood pressure of medullary ischemia and the stimulation from the tantalum wire were additive, they believe that the hypertension of increased intracranial pressure is due not only to decreased medullary blood flow but also to the mechanical pressure of high cerebrospinal fluid tension.

a hyperirritable state of the vasomotor centers in essential hypertension. He found that inhalation of carbon dioxide causes three times as great a rise in blood pressure in patients with essential hypertension as in normals. He also observed that protracted deep breathing with resultant depression of the carbon dioxide tension of the blood causes a striking fall in blood pressure in essential hypertension but not in normal controls. Since these effects were not obtained in hypertension induced by epinephrine, Raab believes that they *are of central origin*, a corollary that, while quite probably true, does not follow unconditionally from the evidence presented. Raab also found that in nephritic hypertension the reactions to carbon dioxide inhalation and deep breathing were the same as in normals. His conclusion is that the vasomotor centers are hyperirritable in essential but not in nephritic hypertension. In a few patients tested by the writer there was no definite difference in the effect of inhalation of carbon dioxide on the blood pressure patients with essential and nephritic hypertension. In a subsequent investigation Raab reaches the conclusion—largely on the basis of the already known facts, which he verifies, that oxygen want and acid perfusion stimulate the medullary vasomotor centers—that essential hypertension results from spasm or sclerosis of vessels in the brain stem so that local oxygen want and accumulation of lactic acid result.

A number of investigators have described lesions in the region of the vasomotor center in the medulla in essential hypertension. Riebold[304] studied a case of hypertension of twenty years' standing in which necropsy revealed no notable renal lesions, but there was severe cerebral arteriosclerosis with areas of softening. He believed that arteriosclerotic changes in the vessels at the base of the brain with consequent lesions in the medulla are responsible for many instances of hypertension—a conception for which he presented no convincing support. Veelen[305] found severe degenerative changes in the ganglion cells in the region of the vasomotor center in an instance of hypertension. Bordley and Baker[306] also observed arteriosclerotic changes in the small vessels of the medulla in individuals with persistent hypertension. On the other hand, in a later exhaustive investigation Cutler[307] found that in more than one-half of the cases with hypertension sclerosis of the vessels in the medulla is absent. Ruehl[308] also found no evidence that the medulla oblongata in hypertensive individuals suffers notably from deficient circulation; he observed the region of the vasomotor center to be morphologically intact. And Baker's[310] studies showed that, while the larger cerebral arteries often present definite arteriosclerotic narrowing, the average small cerebral artery in long-standing essential hypertension shows little change; only when the process enters the malignant phase do the small cerebral arteries show intimal and medial alterations. Likewise the writer[311] found arteriolosclerosis in the brain in only 6 of 31 cases of long-standing essential hypertension; however, only a few areas were examined in each case.

It does not seem that adequate evidence has been presented that organic lesions of the blood vessels supplying the vasomotor center are the cause of essential hypertension; in fact, the above-mentioned negative findings speak strongly against this view. Extreme arteriosclerosis of the circle of Willis and other large cerebral arteries, with widespread areas of softening

syndrome, including hypertension. It was mentioned above that hypertension has been produced by damaging the hypothalamus. However, the observations of Birchall *et al.*[301] on the diuretic response to injected saline afforded no evidence of impaired hypothalamic function in essential hypertension.

Participation of the Central Nervous System in Essential Hypertension.—In many patients with essential hypertension, especially in the clinically early stages, symptoms plausibly attributed to a cerebral origin dominate the picture. Most often the symptoms in question closely resemble those of a psychoneurosis, such as restlessness, irritability, emotional instability, fleeting headache, sweating, flushing, palpitation, coldness of the extremities, etc. Page pointed out that in some cases the clinical picture is one that can be explained on the basis of diencephalic stimulation (page 800). In most patients in the early stages of essential hypertension, not only the subjective symptoms but also the blood pressure show great fluctuations with periods of seeming normality. Moreover, both symptoms and blood pressure are often influenced by emotion.

These clinical observations suggest a nervous origin of essential hypertension and have led to the widespread designation as *neurogenic hypertension* of essential hypertension in which the nervous symptoms are prominent. The appellation neurogenic hypertension has also been applied to the earlier fluctuant stages of essential hypertension regardless of whether or not symptoms are present. That neurogenic hypertension actually exists is demonstrated by the hypertension in the organic diseases of the central nervous system mentioned in the preceding section, by the emotional hypertension to be discussed below, and by the experimental hypertension following section of the moderator nerves. But that the same is true of essential hypertension still has in it an element of assumption. A clinical picture resembling a psychoneurosis in a patient with essential hypertension does not prove the elevation in blood pressure to be of nervous origin. Similar symptoms are often present during the climacteric, and yet their relief by an estrogen testifies to their endocrine and not nervous origin. Actually, a considerable proportion of the cases designated as neurogenic hypertension are women in the climacteric period. While it is quite probable that a large contingent of the cases included in the concept of essential hypertension originate in the nervous system, this has not yet been proved beyond doubt, and until such proof is forthcoming, the application of the term neurogenic hypertension to patients with essential hypertension is not beyond cavil.

Probably largely influenced by the evidence that the hypertension of increased intracranial pressure is due to stimulation of the vasomotor center, various investigators have regarded essential hypertension as originating in alterations in this part of the brain. Such a conception was long ago advanced by Monakow,[302] who, with little supporting evidence, attributed hypertension to a disturbance in the central regulation of blood pressure, the vasomotor centers are hyperirritable and "set" at a higher level, much as the thermo-regulatory centers are thought to maintain the body temperature at a higher level in fever. In harmony with Monakow's hypothesis are the observations of Raab,[303] who believes that his experiments indicate

block of the carotid sinus produces in normotensives an average rise in blood pressure of 80/55 mm and in heart rate of 53 beats per minute in essential hypertension the average rise was 82/45 mm and 51 beats and in malignant hypertension 101/53 mm and 50 beats Since the carotid sinus nerves are thus proved to function normally in hypertensives why does not the elevation in intra arterial pressure lower the blood pressure and heart rate through the carotid sinus reflex? This has been explained by Kezdi[338] on the basis of experiments by Hauss[339] *et al* which show that elevation of pressure within the carotid sinus does not diminish the blood pressure of the dog if expansion of the carotid sinus is prevented by rigid encasement they conclude that intra arterial pressure stimulates the receptors in the wall of the carotid sinus by stretching of the arterial wall Kezdi believes that in hypertensives the elasticity of the arterial wall is diminished so that the extent of stretching by the increased intravascular pressure is only the same as in normotensives and the stimulation of the carotid sinus receptors is consequently the same

The suggestion that arteriosclerotic changes in the arch of the aorta and the carotid sinus might produce hypertension is not supported by the investigations of Keele[340] who found no relation between the degree of arteriosclerotic involvement of the carotid sinus and aorta and the presence of hypertension

Although there is thus no evidence that essential hypertension originates as a disorder of the autonomic nervous system many formerly took for granted that whatever the origin of essential hypertension the arteriolar constriction which is the immediate mediator of the rise in pressure is produced by augmented tone of the sympathetic vasoconstrictor nerves Such sympathetic stimulation is responsible for the neurogenic hypertension produced by increased intracranial pressure or section of the moderator nerves for in both sympathectomy lowers the blood pressure to normal (Bacq Brouha and Heymans[341] Grimson[342]) Similarly experimental neurogenic hypertension is abolished by benzodioxane dibenamine or other adrenolytic and sympatholytic agents (cf Nickerson[343]) Contrariwise hyperactivity of the vasoconstrictor nerves is not an essential component of the mechanism of renal hypertension for the latter is not prevented or abolished by sympathectomy (page 321) or dibenamine or other adrenergic blocking agents (Wilburne[344] *et al* Katz and Friedberg[345])

Contrary to what might have been anticipated the results of sympathectomy and the administration of sympathetic blocking agents in essential hypertension have not brought unequivocal evidence that the tone of the sympathetic vasoconstrictor nerves is increased Even total sympathectomy lowers the blood pressure in only some patients with essential hypertension and in almost all of these the blood pressure subsequently rises The same is true of sympathetic blocking agents (Chapter 29) Moreover in those cases in which sympathectomy decreases the blood pressure the nature of the depressor mechanism is not clear and seems to be complex not only arteriolar dilatation is concerned but it also appears that relaxation of the postarteriolar stream bed decreases the venous return to the heart The results of sympathectomy and sympathetic blocking agents therefore do not afford an unequivocal assessment of the

is often found where there was no hypertension during life And it has been seen that arteriolosclerosis is quite probably a concomitant or consequence of hypertension there is no reason to assume that such lesions in the cerebral arterioles have any different pathogenesis than in other organs Moreover they are frequently completely absent in essential hypertension

There seems to be no evidence that the proliferative and degenerative changes in the cerebral capillaries described by Scheinker[311] in essential hypertension cause the rise in blood pressure the writer doubts their specificity and believes they are far from constant

To summarize what is known about the causation of hypertension by organic lesions of the central nervous system *Observations in bulbar poliomyelitis and other diseases prove that organic lesions of the central nervous system can produce severe and protracted hypertension But the existence of such lesions in the usual essential hypertension has not been demonstrated* Of course this does not prove that the lesions do not exist, the field is in urgent need of further investigation by modern neurohistological methods Nor is there evidence that cutting down of cerebral blood flow by arteriosclerosis or arteriolosclerosis plays a causative role in essential hypertension

The Autonomic Nervous System —Because of the great importance of the vegetative nervous system in the physiological regulation of the circulation it has often been thought that essential hypertension might originate in this system Da Costa and Longstreth[334] long ago claimed to have found lesions of the sympathetic ganglia in Bright s disease which they believed to be responsible for the renal lesions and cardiac hypertrophy So far as I am aware these findings were never confirmed Dember s[335] histological studies of the splanchnic nerves and sympathetic ganglia removed at 20 sympathectomies on hypertensive patients disclosed no abnormalities Contrary to some earlier findings of increased cholinesterase activity of the serum in hypertension which had been interpreted as evidence of autonomic imbalance Vorhaus[336] found the cholinesterase activity normal

Following the discovery of the enormous importance of reflexes originating in the carotid sinus and arch of the aorta for the regulation of the blood pressure (page 303) the possibility that hypertension results from derangement of this reflex mechanism had to be taken into consideration We have already referred (page 304) to the important work of Koch and Mies who produced chronic hypertension in animals by severing the afferent nerves from the aorta and carotid sinus other investigators have since accomplished the same However there is no evidence that this form of experimental hypertension has any relation to essential hypertension in man

While the rise in blood pressure in essential hypertension is the result of arteriolar constriction and not of increased cardiac output that in section of the moderator nerves seems to be due primarily to increase in cardiac output Carotid sinus hypertension contrary to the essential variety is always accompanied by extreme tachycardia It was seen on page 304 that external pressure on the carotid sinus has much the same effect on normotensives and hypertensives Indubitable evidence that the function of the carotid sinus nerves is intact in hypertension is afforded by the experiments of Lampen[337] and his co workers They found that bilateral procaine

panied by fall in pressure Wolff et al further observed that when anxiety and conflict are evident and overt the rise in pressure is due to increased cardiac output while when the manifestations of conflict are suppressed both peripheral vasoconstriction and augmented cardiac output participate in the pressor response The second pattern with vasoconstriction is characteristically invoked by patients with essential hypertension It is interesting that contrary to emotional stress, physical exercise does not elevate the blood pressure more in hypertensives than in controls (Taylor et al[20]) Pfeiffer and Wolff found that both normotensives and hypertensives react to a stressful interview with renal vasoconstriction resulting in decreased renal blood flow with an increased filtration fraction These fundamental observations of Wolff and his associates show that both normals and hypertensives react to emotional stress with the same circulatory pattern of response—rise in blood pressure with decreased renal blood flow—but the intensity and duration of the reaction is greater in the hypertensive

2 *Overtly Emotional Initiation or Aggravation of Clinical Hypertension* — A variety of clinical observations shows that emotion may initiate hypertension of more than momentary duration or aggravate pre-existent hypertension In some though apparently exceptional instances of depressive states in insanity there is marked hypertension which may disappear with recovery from the melancholia (Mueller) I have also seen such cases Patients with essential hypertension as do so many with other diseases often state that their symptoms appeared after an emotional upset It is a fairly common clinical observation that in patients with hypertension worry anger fear anxiety and other emotions may cause a considerable rise in blood pressure which disappears if the agitated state is pacified The following striking instance of marked hypertension resulting from an emotional state was long ago published by O Mueller[23]

A man of pyknic arthritic habitus entered the clinic with a systolic blood pressure of 260 mm and occasional attacks of pulmonary edema Corresponding to the stasis there was a trace of albumin in the urine and diuresis was deficient (bed rest and the usual chemical means were without effect) One day the man who was of a very amiable nature stated that he had behaved unfairly to his wife and this situation depressed him extremely In the hospital everything was successfully explained to the wife which resulted in the systolic blood pressure dropping from 260 to 200 mm the diuresis becoming satisfactory disappearance of pulmonary edema and proteinuria and the patient moved about like a healthy person without any deleterious consequences The excretory functions of the kidney were perfectly normal Mueller saw the patient several years later and found him healthy with a blood pressure of 130 mm though the cardiac hypertrophy had not completely disappeared

Observations on large groups subjected to intense emotional trauma show that many of those affected develop rise in arterial pressure of more than momentary duration When Graham[24] examined 695 men from an Armoured Brigade who had had at least a year of desert warfare between four and eight weeks after battle had ceased he found that 27 per cent had asymptomatic diastolic hypertension of over 100 mm Reexamination of

neurogenic element For the same reason, the study of the effect of high spinal anesthesia in essential hypertension (Gregory and Levin,[348] Taylor[349] *et al*) does not offer an index of neurogenic participation

Strong evidence that the tone of the sympathetic vasoconstrictor nerves is not increased in essential hypertension is afforded by the pioneer experiments of Prinzmetal and Wilson[346] and Pickering[347] These investigators measured plethysmographically the blood flow through the hand before and after the activity of the sympathetic nerves had been eliminated by nerve block or warming The increase in blood flow following elimination of the action of the sympathetic nerves was no greater in the hypertensives than in the controls This indicates that the sympathetic tone in the hand is not augmented in essential hypertension else the blood flow would have increased more on elimination of this tone than in controls

This fundamentally important finding of Prinzmetal and Wilson and Pickering—that the tone of the sympathetic vasoconstrictor nerves is not increased in essential hypertension—has recently been buttressed by an independent method by Kowalski[401] *et al* They showed that the effect of tetraethylammonium on peripheral resistance depends on the vasomotor tone and use of this test discloses no increase in neurogenic vasomotor tone in the extremities of hypertensive subjects

Psychic Factors in the Production of Essential Hypertension —Many recent investigators have arrived at the conclusion that psychic factors play an important according to some predominant role in the causation of essential hypertension This point of view was forcefully pioneered by Moschcowitz[31] as far back as 1919 Since then it has been supported by Alexander[313] Weiss[314] Wolff[315] Binger[316] Dunbar[317] and many other investigators of the role of the psyche in disease of the soma With the rise of the concept of psychosomatic disease in the past two decades the interpretation of essential hypertension as a paradigm of such a disease has gained more and more advocates—among internists as well as psychiatrists Principal among the lines of evidence regarded as favoring the psychosomatic theory of the genesis of essential hypertension are the following

1 *The Pressor Effects of Emotion* – It has long been known that various emotions and other mental processes may produce transitory or even long continued elevations in blood pressure Bickel[318] found that mental work intellectual pleasure and displeasure sensual pleasure and displeasure and strained attention all cause a rise in blood pressure if they produce any change at all Stieglitz[319] reported a series of cases in which emotional strain was accompanied by hypertension On the other hand Fischer[320] found that mental exertion unaccompanied by an emotional element as in the solution of difficult chess problems had no notable effect on the blood pressure

Outstanding studies of the effects of emotion on the blood pressure and other circulatory variables have been carried out by Wolff[315] and his associates They find that the blood pressure rises when the normal or hypertensive subject in a stressful interview is resentful because he considers himself menaced or trapped Contrariwise what seems very exceptional in the hypertensive the feeling of being overwhelmed is accom

panied by fall in pressure Wolff *et al* further observed that when anxiety and conflict are evident and overt the rise in pressure is due to increased cardiac output while when the manifestations of conflict are suppressed *both peripheral* vasoconstriction and augmented cardiac output participate in the pressor response The second pattern with vasoconstriction is characteristically invoked by patients with essential hypertension It is interesting that contrary to emotional stress physical exercise does not elevate the blood pressure more in hypertensives than in controls (Taylor *et al*[31]) Pfeiffer and Wolff found that both normotensives and hypertensives react to a stressful interview with renal vasoconstriction resulting in decreased renal blood flow with an increased filtration fraction These fundamental observations of Wolff and his associates show that both normals and hypertensives react to emotional stress with the same circulatory pattern of response—rise in blood pressure with decreased renal blood flow—but the intensity and duration of the reaction is greater in the hypertensive

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A man of plethoric arthritic habitus entered the clinic with a systolic blood pressure of 280 mm and occasional attacks of pulmonary edema Corresponding to the stasis there was a trace of albumin in the urine and diuresis was deficient (bed rest and the usual chemical means were without effect) One day the man who was of a very amiable nature stated that he had behaved unfairly to his wife and this situation depressed him extremely In the hospital everything was successfully explained to the wife which resulted in the systolic blood pressure dropping from 280 to 150 mm the diuresis becoming satisfactory disappearance of pulmonary edema and proteinuria and the patient moved about like a healthy person without any deleterious consequences The excretory functions of the kidney were perfectly normal Mueller saw the patient several years later and found him healthy with a blood pressure of 130 mm though the cardiac hypertrophy had not completely disappeared

Observation on large groups subjected to intense emotional trauma show that many of those affected develop rise in arterial pressure of more than momentary duration When Graham[34] examined 695 men from an Armoured Brigade who had had at least a year of desert warfare between four and eight weeks after battle had ceased he found that 27 per cent had asymptomatic diastolic hypertension of over 100 mm Reexamination of

33 of these hypertensives after two months more freedom from battle anxieties revealed 28 to have a normal blood pressure. Ehrstrom[325] observed that about one-quarter of front line soldiers on the Finnish front had a systolic pressure of over 150 mm. and that over half of these had an elevated diastolic pressure. After the Texas City blast disaster Ruskin *et al.*[326] observed that 103 of 180 injured had a diastolic pressure of over 95 mm. at one time or another; the hypertension seems to have been of brief duration but in extreme cases reached a diastolic level of 140 to 160 mm.

3. *Experimental Emotional Hypertension.*—Of great interest in this connection is the production of hypertension in rats by audiogenic stimulation. Farris *et al.*[327] found that 10 of 12 rats subjected to a minimum of 167 daily exposures to the sound of an air blast developed hypertension while the latter appeared in only 1 of 11 controls. The rats had been tested for emotionality and it was found that while all the emotional air-blasted rats developed hypertension none of the emotional controls did. The blast hypertension developed only in the older rats, which is a similarity to human essential hypertension.

4. *The Personality of the Patient with Essential Hypertension.*—Many who have studied hypertensive patients from a psychological point of view have thought that their observations disclosed a specific type of personality with a characteristic reaction pattern in interpersonal relations as especially prone to develop essential hypertension. Unfortunately the characterizations of the "hypertensive personality" have differed. Thus, Gressel *et al.*[328] cite different investigators who regard the hypertensive personality as characterized by habitual unexpressed or displaced hostility, lifelong emotional lability with frequent depression, anxiety or both, lifelong anxiety, perfectionism, compulsiveness or difficult with authority. Moschcowitz[312] originally described the hypertensive individual as the antithesis of the child in mind and spirit: they do not play, they are irritable and have single-track minds without avocations. While their mental horizon is narrow, within this range they are tense and pursue their aims with a grim desperation. Weiss, one of the earliest protagonists of the importance of emotional factors in the causation of essential hypertension, finds that chronic and repressed rage and anxiety are especially important. Menninger[329] believed that suppressed resentment, hate or fear is of great importance in the causation of essential hypertension. The large majority of Binger's hypertensives had great difficulty in asserting themselves. Wolf and Wolff found that their "hypertensive subjects, often gentle, poised and apparently easy going, were filled with aggressive drive which was tightly restrained by a need to please." Palmer[330] observed in his studies of the personalities of 50 hypertensives that "Originality, special skills and even special interests are conspicuous by their absence. Practicality, objectivity and adaptability are the chief characteristics. The predominant character traits which the physician sees and which the patient recognizes in himself are those with survival value in our competitive cash culture." Gressel and his associates have investigated the correlation between certain personality patterns and hypertension. They found statistically significant degrees of association with hypertension for "obsessive-compulsive behavior" and "subnormal assertiveness

5 *The Early Symptoms* —Emotional instability restlessness irritability and in brain workers inability to concentrate are sometimes among the first symptoms which bring the patient with essential hypertension to the physician Riseman and Weiss[381] and Ayman and Pratt[422] have emphasized that most of the early symptoms of essential hypertension bear a close resemblance to the manifestations of the psychoneuroses The latter investigators who observed symptomatic improvement as a result of simple suggestion in 82 per cent of patients with early essential hypertension hold that the early symptoms associated with the disease are of psychic origin Various and shifting bodily aches and pains (rheumatic pains) are among the common complaints of patients in whom hypertension has recently been discovered and Holmes and Wolff[423] have found evidence that they are due to muscular hypertonicity notably affected by emotion

6 *Occurrence of Essential Hypertension in Advanced Cultures* —It has been seen (page 691) that essential hypertension is largely a disease of advanced cultures This has been attributed to the complex interpersonal relationships characteristic of contemporary Occidental civilization and regarded as compatible with a psychosomatic genesis of essential hypertension

7 *Improvement as a Result of Psychotherapy* —There have been reports of symptomatic improvement and lowering of blood pressure in hypertensive patients under psychotherapy These changes have been attributed to improvement in the emotional status of the patients when anxiety is relieved as a result of extroversion of repressed hostility (Weiss) Wolff and Wolf found that aid by the physician in the adjustment of the life situations of patients with essential hypertension produced symptomatic improvement in about two-thirds of the cases and in between one-fifth and one-tenth was accompanied by reduction of blood pressure to normotensive levels for significantly long periods

8 *Effects of Sleep and Sedation* —In many patients with essential hypertension the blood pressure falls strikingly during sleep and after the administration of large doses of barbiturates

9 *Psychosurgery* —A few results of ablation of portions of the cerebral cortex in hypertensive patients (page 925) have been viewed as compatible with the psychosomatic theory However the observations are too few in number to be significant

The psychosomatic theory of essential hypertension is directly in the main current of the medical thinking of our time Some of the supporting evidence just cited is highly suggestive But there are also strong objections to the theory

1 The writer has examined several patients with essential hypertension almost every working day for twenty five years In this experience I have been impressed by the extreme rarity of ground for the belief that the hypertension had been initiated by a clearly defined psychological reaction Indeed although a high proportion of the patients whom I see in private practice give what seems to me an intelligent anamnesis and notwithstanding careful inquiry into the life situation of each patient I have yet to encounter an instance in which the psychogenic initiation of essential hypertension was unequivocal

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The psychosomatic theory of essential hypertension has not graduated from the status of a theory. Various emotions occasion elevation of blood pressure in both the healthy and hypertensives. In addition to raising the blood pressure they may precipitate or aggravate symptoms in essential hypertension. But that repeated pressor episodes of emotional origin can ultimately induce a self perpetuating hypertensive mechanism has not been demonstrated. That disturbed interpersonal relationship or other emotional disturbance is the *primary* cause of essential hypertension still remains to be proved.

As yet the role of the nervous system, including the psyche, in essential hypertension remains shrouded in darkness.

ESSENTIAL HYPERTENSION AND SELYE'S ADAPTATION SYNDROME

Selye's[330] brilliant studies have brought evidence that any stress affecting large portions of the body elicits—in addition to the specific damage and reaction characteristic of the individual noxious agent—essentially similar functional, biochemical and morphological changes in the vertebrate organism. The totality of these nonspecific changes he calls the *General Adaptation Syndrome*. Among the stresses which Selye studied and on the basis of which he developed his concept of the General Adaptation Syndrome are cold, fatigue, infection, intoxication and emotion. As the designation indicates, Selye believes the General Adaptation Syndrome is a coordinated useful response participating in the defense of the threatened organism. The General Adaptation Syndrome is initiated by stimulation of the hypophysis and the hypothalamic vegetative centers. The mechanism of the mediation of the stimulus from the initiating agent to the hypophysis and hypothalamus is unknown. The hypophyseal activation calls into play a hormonal defense mechanism by discharge of ACTH which in turn results in liberation of adrenal cortical steroids with their important role in resistance. The hypothalamic stimulation unleashes a nervous defense mediated by autonomic nerves, including discharge of epinephrine and nor-epinephrine from the chromaffin cells. The manifold manifestations of the nervous and hormonal stimulation constitute the General Adaptation Syndrome.

Selye believes that intensification, protraction or perversion of the primarily beneficent reactions of the General Adaptation Syndrome are the essential elements in the pathogenesis of many common diseases. He terms these *diseases of adaptation*. Included are notably rheumatic, allergic, hypertensive and arteriosclerotic maladies, as well as peptic ulcer and perhaps psychosomatic disorders. In all of these, constituting the major moiety of the outstanding medical problems of our civilization, Selye adduces considerations indicating the participation of abnormal discharge of cortical steroids brought about by pituitary stimulation and also often of the consequences of autonomic nervous stimulation.

Essential hypertension and glomerulonephritis stand high in Selye's list of diseases of adaptation. Much of his experimental work is concerned with the production of hypertension and arteriolar lesions in rats and other

2 The writer has not been able to differentiate the "hypertensive personality." The descriptions of the personality of the hypertensive patient given by advocates of the psychosomatic theory differ from one another, the characteristics they describe are absent in many hypertensives and present in numerous normotensives. Suppressed resentment, hate and fear—most often described as characteristic of the hypertensive personality—are found in victims of peptic ulcer and many other diseases quite as well as in hypertensives.

3 The fact that, contrary to such diseases as peptic ulcer and Graves' disease, established essential hypertension almost never undergoes spontaneous cure not only does not support a primarily psychogenic origin of the disease but is difficult to reconcile with the latter. This is all the more significant because well established essential hypertension may exist for a decade or more without evidence of irreversible morphologic changes in the kidneys or other organs.

4 While emotion may occasion a rise in blood pressure, there is no evidence that the pressor mechanism thus set in action is self perpetuating. In the observations of Graham cited above, in which hypertension was the result of a year or more of campaigning in the African desert, within a few months the blood pressure of almost all the subjects had returned to normal.

5 In the hypertensive patients seen by the writer who have undergone psychotherapy, the effect on the natural history of the disease has not been such as to indicate a primarily psychoneurotic origin. The fact that a judicious physician can often attain symptomatic relief in essential hypertension by reassurance and other forms of suggestion—and that with the reassurance of the patient the blood pressure often falls strikingly—does not prove that the disease is primarily of emotional origin. Without the help afforded by reassurance in a host of diseases, the practice of medicine would indeed be a burden. The fall in blood pressure during sleep or after sedatives does not indicate the psychogenic nature of essential hypertension; it occurs in health and I have observed it in nephritic hypertension.

The psychosomatic theory of essential hypertension is still *sub judice*. There may be included in our present ill-defined concept of essential hypertension cases of psychogenic nature. But the evidence available at present does not indicate that, in at least the vast majority of cases of essential hypertension, disturbances in interpersonal adjustment play more than a secondary and aggravating role.

Summary.—Protracted hypertension may have its origin in the nervous system. Interruption of the moderator nerves, appropriately situated lesions of the central nervous system, and interference with the blood flow through the medulla may each call forth neurogenic hypertension. However, there is no evidence that any of these mechanisms plays a primary part in the pathogenesis of essential hypertension. Nor has it been demonstrated that essential hypertension is mediated through increased tone of the vasomotor nerves. The finding that essential hypertension may persist after as complete a sympathectomy as feasible indicates that participation of the nervous system is not a *sine qua non* for the perpetuation of the disease.

The results of experimental investigations of the effect of lead on blood pressure are contradictory. Fouts and Page[354] observed no change in blood pressure in a dog fed large amounts of lead for one hundred and sixty weeks and in another followed for a much shorter time. Wirtschafter[355] did not observe hypertension in rabbits given lead. Contrariwise, Beckmann[356] did produce hypertension in rabbits with lead. In rats Griffith and Landauer[357] found that all four of their rabbits which survived the administration of lead for forty days became hypertensive.

Transitory hypertension may occur during acute episodes of lead poisoning. According to Vaquez[358] Stoll had observed in the eighteenth century that the pulse is very hard during lead colic. At the time that plumbism was very common Pal[359], Vaquez and others found that hypertension often accompanies lead colic. I observed the same association; the hypertension was not due solely to the pain, for it was present when the latter was controlled. Traube[357] noted and Vaquez confirmed that lead encephalopathy occurs almost invariably in the presence of marked hypertension. In an instance of lead encephalopathy observed by Ménétrier[358] the systolic pressure reached 300 mm. There is evidence that acute lead hypertension is due to vasoconstriction. Elschnig[359] observed ophthalmoscopically the obliteration of the retinal arteries in a painter who became suddenly blind during an attack of lead colic. On page 302 was cited the observation of Labadie-Lagrave and Laubry in a case of acute lead poisoning with great hypertension in which amaurosis was relieved as the blood pressure was lowered by amyl nitrite. Vaquez and Pal interpret their observations as indicating that lead colic is the result of spasm of the mesenteric vessels with ischemia of the intestine, though it is also possible that the colic is primarily due to spasm of the intestinal musculature. Tscherkess[360] showed in rabbits that lead stimulates the smooth muscle of the vessel wall.

Older observers described a high incidence of hypertension in chronic lead poisoning. Allbutt[361] found high arterial tension the rule in chronic lead poisoning and Harris[362] noted hypertension in 39 per cent of painters with symptoms of lead intoxication. Ollivier[363] pointed out in 1863 that proteinuria and granular kidneys are common in chronic plumbism. Dickinson[364] found that of 42 workers in lead trades who died from disease or accident 26 had granular kidneys. The lesions appear to be the results of arteriolosclerosis (cf. Brogsitter and Wodarz[365]).

More recent observations do not confirm this high incidence of hypertension and renal disease in chronic lead poisoning. Thus the careful study of Greenfield and Gray[366] revealed that of 40 patients with either acute lead poisoning or an acute exacerbation of chronic plumbism, only 3 had hypertension. And in these 3 the hypertension disappeared within two or three weeks after removal from exposure. Belknap[367] did not observe an unusual incidence of hypertension in workers long exposed to lead.

Quite probably many of the cases attributed by older clinicians to lead were actually instances of essential hypertension which had no connection with the exposure of the patient to lead. However, some of the difference between older and more recent observations on the occurrence of hypertension and renal disease as a result of plumbism may well be due to the

animals by exposure to cold and other forms of nonspecific stress and by the injection of adrenal cortical steroids or the stimulation of their formation by pituitary hormones. In rats after preliminary unilateral nephrectomy and the use of 1 per cent NaCl as drinking water Selye found that desoxycorticosterone acetate produces hypertension, cardiac hypertrophy, arteriolar lesions ranging from hyalinization to periarteritis nodosa and nephrosclerosis with glomerular hyalinization. Similar effects were readily elicited in young chicks. Contrariwise hypertension and arteriolar lesions were produced by this procedure only irregularly and with large doses of DOCA in the dog, guinea pig, hamster, monkey, mouse and cat. Selye found that administration of DOCA to rats on a sodium free diet does not result in hypertension, vascular lesions or nephrosclerosis. Selye believes that DOCA produces hypertension largely through the intermediacy of the kidney; he cites experiments in which such hypertension in the rat is prevented by bilateral nephrectomy (*cf* however page 710).

On the basis of these and many other considerations (pages 558–576 of his recent book[380]) Selye believes that most clinical forms of hypertension are due to excessive stimulation by various types of stress of the normal adaptive reactions of the body which constitute his General Adaptation Syndrome. The stress produces the hypertension through the intermediacy of ACTH and adrenal cortical steroids or it may result through nervous mechanisms with adrenergic stimulation.

Selye's conception of essential hypertension as an exaggeration of the normal defensive mechanisms which he collectively terms the General Adaptation Syndrome is closely allied to the psychosomatic theory of the disease. It constitutes an integration of beliefs held by many in various forms that aberrations in the activities of the adrenal cortex, the adrenal medulla, the adeno-hypophysis or the autonomic nervous system call forth the rise in arterial pressure. The evidence summarized in the preceding sections indicates that the part played by these organs individually or collectively in essential hypertension has not been established. That essential hypertension is actually an exaggeration or perversion of the same pituitary adrenal or hypothalamic autonomic mechanisms which participate in the normal defense against stress also remains to be demonstrated. Nevertheless the suggestion constitutes a thought provoking working hypothesis and may help canalize research along fruitful lines.

MISCELLANEOUS AGENTS WHICH HAVE BEEN CONSIDERED IN RELATION TO THE ETIOLOGY OF ESSENTIAL HYPERTENSION

Lead.—Clinicians of former generations accepted lead among the causes of Bright's disease. In recent years however the causation of hypertensive and renal disease by plumbism has been seriously questioned. In this connection it should be borne in mind that lead poisoning has decreased enormously in frequency in recent years. I have not seen lead encephalopathy in twenty years. Nevertheless there seems little doubt that lead was formerly incorrectly incriminated in many instances of hypertensive disease.

alcohol to be etiologically significant in three-quarters of the cases of granular degeneration of the kidney in Edinburgh. But Dickinson[250] pointed out that Christison did not show that the incidence of intemperance in those with renal disease was greater than in the other inhabitants of Edinburgh. Dickinson was very skeptical of the role of alcohol in the production of renal disease; he found that the incidence of diseased kidneys was no greater in those who died of delirium tremens than in those who died of accident, nor was it higher in those engaged in the liquor traffic than in persons with occupations less predisposing to intemperance. Bruger's[251] careful survey disclosed no evidence that alcohol is deleterious to the kidneys or blood vessels.

The principal variety of cases of hypertension which has been considered as due to alcoholism is that formerly known as "idiopathic cardiac hypertrophy"—the "Munich beer heart" and the "Tubingen wine heart"—which are now known to have been instances of essential hypertension. But it must be remembered that in these cases the chronic alcoholism was accompanied by excessive ingestion of food and fluid usually resulting in obesity, all of which are factors that may play a part in bringing out hypertension in predisposed individuals. It is therefore far from evident that alcohol as such played any part in causing the hypertension in these cases of beer and wine heart.

Most later authors attribute little or no significance to alcohol *per se* in producing hypertension. Fahr[252] does not believe that alcohol is a factor of any importance in causing either renal or vascular disease. Allbutt[253] was evidently skeptical of the significance of alcohol, though he thought that gourmands are more susceptible to hypertension if they add intemperance in alcohol to overindulgence in food. I have not seen any evidence that chronic alcoholism predisposes to essential hypertension. At one time I had considerable experience with alcoholic derelicts in New York City, most of them elderly men at the time of life when essential hypertension appears, but the tendency was to low rather than high pressures. Nor is hypertension common in patients with portal cirrhosis. In an anatomical investigation Wegelin[254] found a low incidence of renal arteriolosclerosis and cardiac hypertrophy in individuals with cirrhosis of the liver attributable to alcohol. Most often alcoholics have good kidneys and blood vessels, though the kidneys are often rather large, presumably hypertrophy due to increased work and akin to the renal hypertrophy of animals on protracted high protein diet.

Intestinal Auto-intoxication.—Huchard[255] thought that the absorption of toxic substances from the intestine plays a large part in the production of essential hypertension, and early in this century a voluminous literature on the subject accumulated, which will be found summarized in Allbutt's[256] book. It is true that pressor amines are formed in the bacterial putrefaction of protein and that certain quantities of such substances are present in the intestinal contents. But so far as I am aware there is no tangible evidence for the attractive hypothesis which Abel[257] thought might lead to the solution of important problems of vascular and renal pathology, that intestinal auto-intoxication is concerned in the pathogenesis of essential hypertension. This conclusion is substantiated by the statistical investiga-

modern protection of workers in lead industries Formerly chronic lead poisoning was very common Nowadays it has become rare as a result of the precautions taken Moreover, if a worker develops any indication of plumbism he is promptly removed from further exposure Formerly, the victims of chronic lead poisoning returned again and again to their work In New York City, at present, lead intoxication is of negligible significance in the causation of *hypertension* and renal disease

Tobacco —Huchard[68] ranked tobacco prominently among the causes of hypertension and high blood pressure was formerly one bogie flaunted by the anti-smoking propagandists Nevertheless there is no convincing evidence that smoking contributes to the production of chronic hypertension It is true that in pharmacological experiments nicotine raises the blood pressure through stimulation of both the vasoconstrictor center (Pilcher and Sollmann[369]) and the peripheral autonomic ganglia (Hoskins and Ranson[370]) Dixon[371] found that the smoking of a Manila cigar by a novice causes a rise of 20 to 25 mm in systolic pressure which is followed after one-half hour by a sharp fall In veteran smokers however he found that smoking has little effect on the blood pressure John[372] noted a rise in diastolic pressure after the smoking of 2 cigars or 10 cigarettes Mathers *et al*[373] observed that in habitual smokers smoking 2 standard cigarettes produced an average rise of 14 7 mm in systolic and 8 mm in diastolic pressure, the corresponding figures for low-nicotine cigarettes were 11 4 and 5 4 mm In 6 healthy habitual smokers under basal conditions Roth[374] found that smoking 2 standard cigarettes was followed by an average rise of 19 mm systolic and 14 mm diastolic smoking corn silk cigarettes or puffing unlighted standard cigarettes had no effect Hines and Roth[375] found that an especially pronounced rise in blood pressure follows smoking in individuals in whom a hyperreactive vascular system is revealed by an excessive pressor response to immersion of an extremity in cold water

Despite these transitory effects the fact that most men who have smoked excessively for many years have normal or even low blood pressure shows that smoking *per se* does not cause hypertension In fact Lauder Brunton[376] went so far as to say that If in a strong healthy man one found the tension was about 100 or below and he was told he smoked too much in 19 cases out of 20 it would be correct I have also often noted hypotension in inveterate smokers though of course such individuals are by no means immune to hypertension Thompson and Sheldon[377] found that even in persons with hypertension smoking does not have any uniform effect on the blood pressure the number of patients in whom smoking decreased the arterial tension not differing greatly from the number in whom the blood pressure rose

It would therefore seem that whatever may be the damage done to the circulatory apparatus by smoking it is not effected through the medium of hypertension

Alcohol —Alcohol of course has been reckoned among the causes of essential hypertension as it has been considered to be at the root of so many afflictions Bright[378] thought that abuse of alcoholic beverages may play a part in the causation of renal disease and Christison[379] held

Summarizing, it may be stated that there is no evidence that syphilis has any part in the causation of essential hypertension. Nor is there any evidence that syphilis ever causes hypertension to enter the malignant phase (page 821).

Other Infections.—It was formerly occasionally stated that essential hypertension results from old infections, or is a manifestation of focal infection. There is no evidence for these views. Walker and O'Hare[20] studied the comparative incidence of past infections in 400 patients with hypertension and in 400 hospital inmates with normal blood pressure. There was no notable difference between the two groups. I have never seen any effect on the blood pressure of hypertensive patients from the removal of infected teeth, tonsils or other foci. It was mentioned above that tuberculosis is uncommon in hypertensive patients and when it does occur it is usually extremely chronic with great tendency to fibrosis and healing.

Allergy.—Essential hypertension has also been considered to be a manifestation of allergy. This view is held by Waldblatt,[296] who observed hypertension in members of allergic families who were sensitive to food and other allergens. He states that the blood pressure fell on removal of the allergens in question and again rose on repeated exposure. Bienstock[297] also regards essential hypertension as due to sensitization to animal proteins. On the other hand Cohen *et al.*[299] found that in 3 hypertensive patients with allergic symptoms, the control of the latter had no effect on the hypertension. In view of the frequency of such allergic diseases as asthma and hay fever, as well as of essential hypertension, the occasional association proves nothing. Actually there seems to be no good evidence indicating that essential hypertension is a manifestation of allergy in the usual sense of the term. It has seemed to me that hay fever, bronchial asthma and other allergic manifestations are less frequent in essential hypertension than in the general population.

GENERAL DISCUSSION OF THE ETIOLOGY OF ESSENTIAL HYPERTENSION

From the above survey it is seen that despite countless investigations and a considerable number of facts revealed by them, we are as yet very much in the dark as regards the causation of essential hypertension. However, some progress has been made. The available evidence points to participation of three categories of pathogenetic factors in the causation of essential hypertension.

1. *Genetic Influences.*—In at least the large majority of instances, essential hypertension arises on the basis of an inherited predisposition. The statistical investigations cited above show beyond doubt that there is a strong hereditary element in essential hypertension and that the disease tends to occur in individuals of sthenic bodily habitus—itself an inherited characteristic. The more opportunity I have to study the family history of patients with essential hypertension the more convinced I am that at least most of them are genetically preordained to their affliction.

tion of Alvarez *et al*[388] who found no correlation between constipation and hypertension, in fact they noted that in women constipation tends to be associated with low blood pressure.

Syphilis.—In older works, syphilis was almost invariably accorded a prominent place among the causes of "chronic interstitial nephritis." Soon after the introduction of the Wassermann reaction, there were many attempts to incriminate lues as an important factor in the etiology of essential hypertension. Thus, Stoll[389] obtained positive Wassermann or luetin reactions in 43 of 50 patients with hypertensive disease. He considered hypertension as one of the commonest manifestations of congenital lues, a view for which there is no evidence whatsoever. Amblard[390] found syphilis in 78 per cent of hypertensive subjects. Grenet *et al*[391] regarded syphilis as a common cause of essential hypertension; they give an exhaustive description of what they term "hypertension artérielle syphilitique solitaire." Gallavardin[392] also considered syphilis among the important causes of hypertensive disease. He pointed to the frequent coincidence of hypertension with syphilitic aortitis, considering both the aortic and the renal lesions of syphilis causation (*nephro-aortite syphilitique*). Fahr[35] believed that some cases of the malignant phase of essential hypertension (his malignant sclerosis) are of syphilitic origin. He found evidence of lues in 10 of 40 cases of malignant sclerosis though the Wassermann reaction was negative in 4 of these 10.

Despite these findings I find no actual evidence that syphilis plays any part in the causation of essential hypertension. At the Montefiore and Mount Sinai Hospitals I did not find the incidence of positive Wassermann reactions greater in essential hypertension than in the general hospital population. Horine and Weiss[393] found practically the same incidence of syphilis in 666 patients with essential hypertension and 2000 non-hypertensive individuals. Nor does the clinical history or physical examination reveal a notably high incidence of syphilis in hypertensive patients. I can confirm Gallavardin's observation that the combination of syphilitic aortitis and true (diastolic) hypertension was formerly not uncommon; there were 12 such cases within less than two years at Mount Sinai Hospital, but this does not prove that the hypertension in these patients was due to syphilis. Almost all the patients with both diastolic hypertension and luetic aortitis were negroes or Puerto Ricans in whom at the time the incidence of syphilis was high. In recent years with the decreasing frequency of syphilis luetic aortitis has become a rarity in the clinical material I have seen but there is at least as much essential hypertension as ever. It is possible, though not proved, that hypertension predisposes to the localization of syphilis in the aorta. I have not seen any effect of antisyphilitic treatment on hypertension in syphilitic subjects, a result which is in substantial agreement with the findings of Levinson[394] though he states that occasionally the blood pressure does drop somewhat. On rare occasions amyloid contracted kidney resulting from syphilis leads to renal hypertension but this has no bearing on the etiology of essential hypertension. It is conceivable that the rare sclero-gummatous disease of the kidney might lead to renal hypertension but I am not aware of any actual case of this nature.

pluralistic nature of essential hypertension is correct it is to be hoped that the next years will see the differentiation of the individual pathogenetic entities Then the term essential hypertension the chief virtue of which is as a confession of ignorance, will retain only historical significance

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But important as is the recognition of the genetic element in essential hypertension, it discloses only one aspect of the actual nature of the condition and apart from hypothetical eugenic considerations, hardly points the way toward solution of the therapeutic problem What the clinician wants to know is the location and characteristics of the inherited abnormality in structure or function which produces the elevation in blood pressure and how the actual hypertension is precipitated in the genetically conditioned individual

2 *Environmental Agencies* —There are strong indications that essential hypertension is at least more common in those living under the conditions of modern Western civilization What in this culture favors the development of essential hypertension is unknown One unproved possibility is that the complex and so often frustrating interpersonal relationships of Occidental civilization favor the development of hypertension through psychosomatic mechanisms Also worthy of consideration is the possible role of the abundant lipid and protein content of the diet which modern industrial civilization affords to a far higher proportion of the population than does any other social structure The evidence is good that chronic undernutrition decreases the incidence of essential hypertension in a population

3 *Pressor Mechanisms* —In this chapter evidence has been reviewed suggesting the possibility of renal, endocrine and nervous factors in the pathogenesis of essential hypertension Another obvious possibility—that of primary disease of the arterioles with increase in their intrinsic state of contraction or reactivity to nervous or humoral pressor influences—has been little studied In the discussion of each of the foregoing after presentation of evidence bespeaking its possible participation in essential hypertension, other considerations were adduced militating against its primary pathogenetic role in at least some of the cases

The possibility arises that essential hypertension is not an entity but rather embraces several pathogenetically distinct diseases having in common chronic hypertension and its consequences Such a pluralistic conception is not without attraction to the clinician In practice one is often impressed that for years the clinical picture of many patients with essential hypertension mimics a psychoneurosis in others each of several members of a hypertensive family has an "apoplectic habitus," the picture is dominated from the start by violent headaches and evidences of cerebral arteriosclerosis and all succumb to cerebral vascular accidents still others with essential hypertension have so many stigmata of an endocrine disturbance akin to the Cushing syndrome that one goes to great pains to rule out the latter, and there is a further group of patients with essential hypertension in whom evidence of renal damage is present from early in the course and who quickly go on to renal insufficiency The nervous system the endocrine glands the intrinsic functions of the arterial walls and the kidneys probably all participate in the regulation of the blood pressure and it may well be that included in "essential hypertension" are discrete conditions initiated by disturbances in each of these regulatory coefficients of the arterial pressure But despite their differing origin all of these disturbances would tend toward a common clinical picture because of the existence of arterial hypertension and its consequences If this speculative conception of the

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Chapter

26

ESSENTIAL HYPERTENSION
III CLINICAL PICTURE

ESSENTIAL hypertension appears before the physician under many guises Onsets symptoms and course are protean The clinical manifestations may be those of cardiac failure of angina pectoris of an organic disease of the brain of a psychoneurosis of renal disease or of disorders of various other organs Or there may be disturbances emanating simultaneously from several organs so that very complex clinical pictures result

At times the first manifestation of the disease is a fatal apoplectic stroke or the malady may pursue a malignant course leading to death within a few months after the initial symptoms But far more often after an insidious onset essential hypertension runs an exquisitely chronic course extending over years and there are many cases in which marked hypertension lasts for decades without ever doing the individual any discernible harm until he finally dies of an unrelated disorder

It is to the introduction into every-day practice of the sphygmomanometer that we owe the recognition of the common pathogenetic factor underlying these dissimilar clinical pictures which were formerly considered as primary diseases of the particular organ from which the outstanding symptoms emanate Only within recent decades do the textbooks of medicine contain a special section on essential hypertension In older works the description of the clinical phenomena of essential hypertension is to be found widely scattered under the headings of chronic interstitial nephritis myocarditis cerebral apoplexy arteriosclerosis etc

Varieties of Symptoms in Essential Hypertension.—In the decade-long course of essential hypertension symptoms of various origins develop Clear differentiation of the mechanism producing the symptoms when feasible is very important for prognosis and treatment The principal categories are

1 *Symptoms Due to Hypertension per se* —These symptoms are alleviated when the blood pressure falls either spontaneously or as a result of sympathectomy or other treatment Among the truly hypertensive manifestations are some (not all) forms of headache left ventricular hypertrophy and that component of cardiac failure which is not due to coronary arteriosclerosis Included also are the characteristic manifestations of the malignant phase of the disease there is good evidence that hypertension produces the arteriolar necrosis which results in renal insufficiency the retinopathy and the cerebral edema of hypertensive encephalopathy Both hypertension and arteriosclerosis are conjoined in the genesis of cerebral hemorrhage

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were between four and five times as apt to have hypertension as those who originally had a low normal pressure.

In the preceding chapter evidence was assembled indicating that at least most cases of essential hypertension are on a hereditary basis. According to this conception the prehypertensive stage of essential hypertension begins with the start of life. As yet, however, such an interpretation of the prehypertensive stage is theoretical, for there is as yet no sure means by which the physician can recognize it in childhood. However, there are many instances in which one can suspect with a high degree of probability that a relatively young person is in the prehypertensive stage of essential hypertension. For one thing, from at least their teens on, most of the individuals in question tend to have a blood pressure in the upper range of the normal. Hines[47] has shown the much greater incidence of subsequent essential hypertension in persons whose previous blood pressure was toward the upper limit of normal, while he found that those with a low blood pressure hardly ever develop hypertension. There is one group, not rare, in which the physician can recognize the prehypertensive stage with much confidence. This consists in youths in their teens with one or both parents hypertensive, of sthenic bodily habitus and a blood pressure of about 130/90 mm. These youths are usually very strong and are often athletes whose parents remark on their great energy and freedom from fatigue. Often ophthalmoscopic examination shows thinning and unusual tortuosity of the arterial blood columns at times when the blood pressure is well within normal limits.

The question of the recognition of the prehypertensive stage by the Hines-Brown cold pressor test is discussed on page 764.

2. *The Stage of Intermittent Hypertension.* —It appears that in most if not all patients with essential hypertension the development of more or less continuous high blood pressure is preceded by a stage of intermittent hypertension. In this stage a blood pressure which is mostly within the normal range is punctuated by periods of hypertension. These may be frequent or far apart. Sometimes the rise in pressure seems attributable to an emotional cause, but more often such a connection is not apparent. The stage of intermittent hypertension may last for months, years or decades; little is known about this because its discovery is usually a matter of chance. During the intermittent stage the large majority of the patients are asymptomatic. However, there may be various symptoms connected with the hypertension, such as vertigo and headache or even, rarely, cerebral hemorrhage. In their study of Army officers Levy[48] and his associates found that subsequent sustained hypertension develops more often in those whose previous records show transient hypertension than in others. My experience has indicated more and more strongly as the years have passed that the large majority of those who have intermittent hypertension later go on to the continuous stage.

3. *The Stage of Continuous Hypertension.* —In the final stage of essential hypertension the blood pressure is high most or all of the time. However, there are hardly any patients with essential hypertension, even after it has entered the malignant phase in which the blood pressure remains at a constant high level practically always, there are considerable fluctuations

2. *Symptoms Due to Arteriosclerosis* —Patients with essential hypertension develop, on the average, much more arteriosclerosis than do normotensives of the same age. The nature of the connection between hypertension and arteriosclerosis has not been established. However, it is important that the arteriosclerotic genesis of symptoms in patients with high blood pressure be recognized, for they are not only not necessarily ameliorated by reduction in arterial tension but may even be aggravated. A high proportion of the cardiac and cerebral manifestations is due to arteriosclerosis, and probably a majority of the patients succumb to them.

3. *Iatrogenic Symptoms* —Knowledge and fear of high blood pressure have become widespread. It is remarkable how often the initial subjective symptoms appear soon after the discovery of hypertension in an individual who until then had felt well. It is obviously important that symptoms of this origin be differentiated.

4. *Coincidental Symptoms* —In a disease that lasts over decades it is to be anticipated that symptoms of wholly independent origin will often appear. Essential hypertension is often discovered in a patient who comes to the physician for another disease. In the Outpatient Department it has been my experience that a majority of the middle-aged women with essential hypertension have symptoms due to the climacteric, a psychoneurosis or other cause, and would usually be better off if the hypertension were unknown to them. On the other hand, in an older hypertensive the early symptoms of bronchial cancer, glaucoma or other ailments may be assumed to be due to the hypertensive disease.

The Stages of Essential Hypertension —Schematically, it is not without value to differentiate three overlapping stages of essential hypertension.

1. *The Prehypertensive Stage* —In this stage the blood pressure is within normal limits at least most of the time. However, under special circumstances in which a pressor stimulus operates, the blood pressure rises more than would be anticipated in health. The most important such circumstances are those which entail emotional stress, notably military and insurance examinations. Time and again one gets the history from a patient with essential hypertension that many years before transitory hypertension was recorded in an insurance examination which was not again found in any of many other examinations for a number of years after. It is probably in individuals in the prehypertensive stage that hypertension accompanies the depressed phases of psychoses or periods of military exposure. I have noted evidence (family history, bodily habitus) that the exceptional instances of hypertension developing shortly after castration in the female affect individuals in the prehypertensive stage. There is similar reason to believe that in an individual in the prehypertensive stage of essential hypertension a lesion of the kidneys or urinary tract which would not otherwise produce high blood pressure does so. Very interesting evidence in support of this conception is afforded by the observations of Hines and Lander.[56] In 284 patients with urologic disease (pyelonephritis, stones, urinary tract infections, neoplasms, etc.) whose blood pressure had been normal on their first visit to the Mayo Clinic and who were reexamined for a urologic disorder on an average of fifteen years later, they found that those whose original blood pressure was in the upper ranges of normal

insomnia irritability and inability to concentrate on work are often among the initial complaints Accompanying these nervous symptoms, there is usually weakness and loss of appetite As a result of failure to use the sphygmomanometer such patients are sometimes considered as neurotics

In other cases the hypertension is first revealed by the symptoms of organic disease of the brain Not rarely an apoplectic stroke resulting from cerebral hemorrhage ushers in the disease in an individual who considered himself perfectly healthy Or the first symptoms may be those of focal cerebral disturbances or mental impairment resulting from multiple areas of softening due to cerebral arteriosclerosis Rarely transitory palsies and other manifestations of hypertensive encephalopathy (Chapter 11) are early symptoms

In an elderly woman with essential hypertension the symptom which first called attention to the disease was sudden amaurosis There were no ophthalmoscopic changes other than the usual arteriosclerosis and the blindness disappeared as suddenly as it came It was evidently a manifestation of hypertensive encephalopathy

Epistaxis is occasionally an early and rarely the first manifestation of essential hypertension hemoptysis is far less common but I have twice seen it as an initial symptom

It is decidedly unusual that uremic manifestations usher in the clinical picture of essential hypertension However this does occur generally in the malignant phase of the disease in younger individuals Nocturia may be an early symptom most often it is a manifestation of cardiac weakness but in other cases it results from impairment of renal function and is then accompanied by polyuria

Paresthesias and pains in the extremities are not very uncommon early features in fact they are the less rare the greater the care with which the history is taken They may occur in the form of intermittent claudication particularly if there is marked arteriosclerosis More common is a feeling of tingling, numbness or coldness in the fingers and toes Or there may be transitory dead fingers In other cases the pains are of a rheumatic nature occurring in the muscles of the extremities trunk and neck

Essential hypertension of a severe variety is occasionally discovered as a result of visual disturbances and the consequent finding of hypertensive retinal changes Not very rarely an ophthalmologist first suspects the presence of hypertension from the retinal arteries while refracting an asymptomatic patient

THE HYPERTENSION

Height of the Blood Pressure —In the large majority of patients with essential hypertension who come to the physician with subjective symptoms of the disease the blood pressure is so definitely elevated that there can be no doubt of the existence of hypertension Usually the systolic pressure is well over 160 mm and the diastolic over 100 mm However one occasionally encounters cases in which the systolic pressure is about 150 mm and the diastolic about 95 mm in a middle-aged person so that without

which even in the severest cases at times approach the normal The stage of continuous hypertension may last for decades

Onset —Nowadays essential hypertension is often discovered fortuitously in the course of a routine insurance, military industrial or other examination Indeed, in recent years a majority of the males—who have more routine examinations than women—with essential hypertension whom I see in private practice state that their hypertension was first noted in a routine examination Essential hypertension is often unveiled in patients who come to the physician because of some other condition, such as the climacteric diabetes obesity prostatism or emphysema

The initial symptoms are of almost infinite variety Often, the patient has had vague symptoms for years before he comes to the physician and it may be impossible to determine whether these were manifestations of the hypertensive disease or due to independent conditions Janeway[1] noted that many hypertensive patients have been subject to migraine since childhood I have also been struck by the frequency with which hypertensive patients say they have had headaches since youth but they are not always of migrainous character Usually these precursory headaches are described as different from the headaches present since hypertension appeared Various clinicians have noted that the first manifestations of the disease often extend back to a relatively young period of life Thus O Hare *et al* believe that Nature very frequently sounds a warning as early as the second decade in life of the possible development of hypertensive disease in the fourth or fifth decade The symptoms which they found often in the early history of patients with essential hypertension were those of vasomotor and emotional instability—nose bleed irritability nervousness and cyanosed hands These were present in the histories of 50 per cent of their hypertensive patients but in only 23 per cent of controls

However these precursory manifestations usually do not bring the individual to the physician and even if they do he can at most but suspect the possibility of future hypertension if there is a well marked family history of the disease or some of the other features of the prehypertensive stage mentioned above As has been seen above definite hypertension appears in the vast majority of instances only beginning with the end of the fourth decade and it is then that the individual with hypertension first comes to the physician The symptoms which bring him may be seemingly trivial or severe recent or of long standing The following are among the most common

Manifestations of cardiac insufficiency are among the most frequent initial symptoms particularly in the obese Dyspnea on exertion or following a heavy meal is perhaps the most common or the cardiac weakness may be revealed first by palpitation precordial oppression swelling of the feet, nocturia, nocturnal attacks of cardiac asthma inability to sleep on the left side etc

Attacks of angina pectoris not uncommonly lead to the discovery of the hypertension Or a myocardial infarction may be the first indication of disease in a hypertensive who states he previously felt well

Nervous symptoms simulating a psychoneurosis very frequently usher in the disease Of these headache is the most common Vertigo tinnitus

How greatly the ordinary activities of life influence the blood pressure in essential hypertension is well brought out by the observations of Smirk[5] and his associates on the basal and what they term the casual and supplemental blood pressures (page 270). In 27 patients with essential hypertension whose casual blood pressure averaged 196/116 the average basal pressure was 151/95; the supplemental blood pressure was proportionately less in normals and in nephritic hypertension. Kilpatrick[6] found that in essential hypertension the basal pressure varies less than the casual reading. He also observed that when a patient with essential hypertension develops heart failure the supplemental pressure falls to even less than in normals; failure to obtain a true basal reading and inability of the heart to respond to pressor stimuli may be concerned.

As a result of the strains of the day, the pressure is usually considerably higher in the evening than in the morning; this difference may reach as much as 50 mm., though generally it is less. As is the case with healthy persons, the blood pressure in essential hypertension falls during sleep. C. Mueller observed that the greater the day pressure, the more pronounced the fall during sleep. He described what he considered the incipient stage of essential hypertension, in which the day pressure is but little elevated, though the night pressure is definitely above the normal (for normal values see page 268). The hypotensive effect of sleep in essential hypertension is often well observed during the sodium amytal test (page 919).

However, there are also many cases of essential hypertension, notably among those in the malignant phase or with heart failure, in which the blood pressure is relatively constant; there is little diurnal fluctuation and all the readings taken over a period of months may be within a range of 30 mm. In such cases, rest and sedation generally have little effect on the blood pressure. It is generally stated (see Ruehl[8]) that the fluctuations are greatest in the early cases and that the pressure *tends* to become fixed as the disease persists. It is undoubtedly true that the most marked fluctuations in blood pressure are generally observed in the younger patients with hypertension; they may even have periods of practically normal blood pressure. Such cases are particularly common in climacteric women. In fact, Ayman[9] obtained one or more *normal* blood pressure readings in 50 per cent of his patients with essential hypertension. It is to be remarked that in the malignant phase of essential hypertension, which generally affects relatively young individuals, it is the rule to find the blood pressure very high and comparatively fixed from the first observation. But there may be fluctuations of great amplitude even in these cases. Likewise, while the blood pressure in old hypertensive patients usually shows but slight lability, there are cases in very old persons which promptly react to bed rest with a sharp drop in pressure.

Fahrenkamp[10] has studied the fluctuations in the height of the blood pressure by constructing curves from several observations a day over a protracted period. Fahrenkamp's findings will be considered in the section on Prognosis.

Various events can cause a fall in the blood pressure of hypertensive individuals. Most often this is due to cardiac failure, particularly when this develops acutely as a result of relatively rapidly evolving coronary

further observation or the demonstration of cardiac hypertrophy the existence of actual hypertension is questionable. Such border-line cases are met with particularly during insurance examinations and in the examination of patients for complaints having no relation to hypertension; they will be discussed further in the section on Diagnosis.

The height of the blood pressure varies greatly in different cases. The values encountered most frequently are around 200 mm systolic and 110 mm diastolic. However the systolic pressure may reach almost 300 mm and extremely rarely exceed it, and the diastolic even surpass 180 mm. In other cases the blood pressure remains for years around 170 mm systolic and 95 to 100 mm diastolic. In some instances the blood pressure rises rapidly; more often the rise is gradual as the patient is watched for years. On the other hand, in very many patients the height of the pressure does not change notably from that found at the first examination even though it is followed for years.

Both systolic and diastolic pressures are elevated but not necessarily proportionately. An important factor in determining the ratio of the systolic to the diastolic pressure is the degree of arteriosclerosis of the aorta and its large tributaries. With severe arteriosclerosis the diminished elasticity of the aorta tends to raise the systolic and lower the diastolic pressure. In these patients pressures such as 220/90 mm are not uncommon. As a result of arteriosclerosis of the aorta the ratio of the pulse pressure to the diastolic pressure tends to be higher in older hypertensives. The effect of heart failure on the blood pressure will be discussed below.

Fluctuations in the Hypertension.—In most hypertensive patients the height of the blood pressure is far from constant. There are great fluctuations not only from day to day but also within a few hours. The fluctuations affect particularly the systolic but also the diastolic pressure. In fact Ayman[3] found that the percentage of fluctuation of the diastolic pressure is as great as that of the systolic. In cases in which the lability of the blood pressure is particularly pronounced there may be fluctuations of as much as 50 mm within a few hours. In such patients, who are found particularly in the young women with climacteric symptoms and those with evidence of emotional instability, physical and especially emotional strains are immediately documented by a rise in pressure. On the other hand mental and physical rest, particularly in bed, results in marked drop in blood pressure which may for a time reach normal though this is not common. These changes are often seen to good advantage in the hospital where it is common to observe a blood pressure which was high on entrance drop strikingly as the patient rests in bed and becomes accustomed to his surroundings.

It appears that the taking of the blood pressure by the physician almost always acts as a pressor stimulus in hypertensive patients who are anxious about the result of the measurement. Ayman and Goldshine[4] found that when patients or their relatives were taught to take the blood pressure at home the readings were often substantially lower than the values obtained in the clinic. Very often the blood pressure reading obtained in the office of the consultant is higher than that of the family physician to whom the patient is accustomed.

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However there are also many cases of essential hypertension, notably among those in the malignant phase or with heart failure, in which the blood pressure is relatively constant; there is little diurnal fluctuation and all the readings taken over a period of months may be within a range of 20 mm. In such cases rest and sedation generally have little effect on the blood pressure. It is generally stated (see Ruehl) that the fluctuations are greatest in the early cases and that the pressure tends to become fixed as the disease persists. It is undoubtedly true that the most marked fluctuations in blood pressure are generally observed in the younger patients with hypertension; they may even have periods of practically normal blood pressure. Such cases are particularly common in climacteric women. In fact Ayman[9] obtained one or more normal blood pressure readings in 40 per cent of his patients with essential hypertension. It is to be remarked that in the malignant phase of essential hypertension, which generally affects relatively young individuals, it is the rule to find the blood pressure very high and comparatively fixed from the first observation. But there may be fluctuations of great amplitude even in these cases. Likewise while the blood pressure in old hypertensive patients usually shows but slight lability, there are cases in very old persons which promptly react to bed rest with a sharp drop in pressure.

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insufficiency. It is to be emphasized, however, that the development of congestive failure is by no means invariably accompanied by a fall in blood pressure (see the following section). Intercurrent febrile illness often lowers an elevated blood pressure, usually, the arterial tension returns quickly to its previous height after the fever subsides, but sometimes the pressure remains lower for a long time. Rest and other therapeutic measures may also lower the pressure, though this is often but transitory.

Blood Pressure and Other Vascular Reactions.—The reactions of the blood pressure to both pressor and depressor influences have been extensively studied in essential hypertension. Therapeutic studies will be considered in Chapter 28. The following will be restricted to the immediate effect of various agents on the blood pressure of hypertensives. O'Hare[11] long ago found that in essential hypertension, as in normals, mental and physical rest lowers the blood pressure while excitement elevates it. Nitrites cause a transitory fall in blood pressure in essential hypertension. However, O'Hare found that the fall caused by nitroglycerin may be preceded by a rise which he attributes to excitement.

The changes in blood pressure following the injection of epinephrine appear to be much the same as in health. O'Hare observed a sharp and marked rise in pressure following the intramuscular injection of epinephrine in hypertension. Pickering and Kissin[12] found no evidence that hypertensive patients are abnormally sensitive to the intravenous injection of epinephrine. Leatherbee and Hines[13] administered by slow intravenous drip a 1 to 250 000 solution of epinephrine. They found a rise in systolic pressure of the same magnitude in hypertensive patients as in those with normal blood pressure, but noted that the diastolic pressure decreased more often in those with hypertension. Elliot and Nuzum[14] observed much the same blood pressure changes following the subcutaneous injection of epinephrine or pitressin in essential hypertension as in health.

The Cold Pressor Test.—Hines and Brown[16] studied in great detail the reaction of the blood pressure when one hand is dipped in cold water. They find that the blood pressure of 98 per cent of individuals with essential hypertension rises much more when the hand is dipped in cold water than does that of normal controls. What is especially interesting is their further observation that many individuals whose blood pressure is normal but who belong to hypertensive families or present evidence of arteriolar sclerosis and whom they therefore regard as potential hypertensives also have an abnormally great pressor response to the stimulus of cold. Hines and Brown regard an abnormally great pressor response in the *cold pressor test*, as it is known, as evidence of a hyperreactive vasomotor system. Following the immersion of one hand to the wrist in ice water (4° to 5° C.) for one minute, they observed average rise of 38 mm. systolic and 32 mm. diastolic in individuals with outspoken hypertension as contrasted with 9 mm. systolic and 7 mm. diastolic in normal controls. A rise of intermediate magnitude was observed in those whom they regarded as potential hypertensives. More recently Hines[17] reports a mean rise in diastolic pressure of 30.9 mm. in 841 patients with essential hypertension and of 13.2 mm. in 1015 subjects with normal or usually normal blood pressure.

From the experiments of Wolf and Hardy[18] it appears that the rise in pressure in the cold pressor test results from the aching pain (cold pain) produced. There is good evidence that the pressor effect is brought about through a nervous mechanism. Reiser and Ferris[19] found that the cold pressor response is eliminated by intravenous injection of tetraethyl ammonium chloride and is reduced by spinal anesthesia in proportion to the extent of the arteriolar bed eliminated from vasomotor control. In a patient with transection of the spinal cord Sullivan[20] found that immersing a hand in ice water elevated the blood pressure while immersion of a foot did not. The rise in blood pressure in the cold pressor test is not mediated by secretion of epinephrine or arterenol for it is not abolished by piperoxane.

When the cold pressor test was first introduced it was hoped that it would disclose potential hypertensives. Support is afforded for this expectation by the long term observations of Hines. He classifies as hyperreactors those whose diastolic pressure rises more than 20 mm in the cold pressor test as normoreactors those with a diastolic rise of 10 to 20 mm and as hyporeactors those with less than 10 mm. Hines found that after fifteen years none of 38 hyporeactors and only 8 of 58 reactors had essential hypertension while this had developed in 31 of 57 hyperreactors. Interesting as are these observations they do not indicate that the result of the cold pressor test is more than one datum to be taken into consideration in evaluating the likelihood of future hypertension. Pickering and Kissin, Alam and Smirk[21] and Hussek and Zohman[22] all found that while a large rise in pressure during the cold pressor test is more common in patients with essential hypertension than in normotensive controls there are many exceptions in both groups and the excursion tends to increase with advancing age in both normotensives and hypertensives. In a seven year follow up study on Air Force officers Armstrong and Rafferty found that the outcome of the cold pressor test affords no indication of the likelihood of the development of hypertension. In his most recent discussion Hines[17] comes to the conclusion that there is no single test of vascular reactivity which suffices to measure the probability of future hypertension in an individual. My experience with a great many cold pressor tests also has not indicated justification for regarding an individual as potentially hypertensive solely on the basis of a pronounced response to the cold pressor test. The results of the test should be used as merely one line of evidence.

The Breath Holding Test.—Ayman and Goldshine[23] test the response to vasomotor stimulation by the effect of holding the breath on the blood pressure. The patient either sits or reclines in a quiet warm room until the blood pressure reaches a constant level. At the end of a quiet expiration he then shuts his lips and compresses his nostrils for twenty seconds. Ayman and Goldshine find the effect of the breath holding test—which does not involve troubling with ice water—on the blood pressure about the same as that of the cold pressor test. Feldt and Wenstrand[24] also observed generally similar responses to the cold pressor and breath holding tests but there were many individuals who were hyperreactors to one and hyporeactors to the other. Gubner and his coworkers likewise obtained similar responses to the cold pressor and breath holding tests and observed

insufficiency. It is to be emphasized, however, that the development of congestive failure is by no means invariably accompanied by a fall in blood pressure (see the following section). Intercurrent febrile illness often lowers an elevated blood pressure; usually the arterial tension returns quickly to its previous height after the fever subsides, but sometimes the pressure remains lower for a long time. Rest and other therapeutic measures may also lower the pressure, though this is often but transitory.

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succumb to congestive failure or coronary insufficiency there were 234 cardiac deaths among 420 fatalities in essential hypertension studied by Bell and Clawson.[a] The enormous importance of hypertension in the causation of heart disease is illustrated by Clawson's finding that of the 9,085 cardiac deaths among 50,730 autopsies, 5,935 had hypertension.

In the following we shall discuss first the manifestations of cardiac compensation and failure and then those of coronary insufficiency. In the natural history of heart failure in essential hypertension three stages can most often be more or less sharply differentiated:

1. Cardiac compensation
2. Isolated left ventricular failure
3. Combined left and right sided failure

Cardiac Compensation in Essential Hypertension. — This is effected by hypertrophy of the heart, the nature of which has already been discussed. It is probable that in the early phases of most if not all cases of essential hypertension there is hypertrophy without notable dilatation of the left ventricle, the concentric hypertrophy of older authors. The pathological anatomist does not often see the hypertensive heart in this state of pure hypertrophy because dilatation supervenes in the vast majority of cases before death. However, such hypertrophy without dilatation is occasionally encountered at necropsy in individuals who died of cerebral hemorrhage resulting from the hypertension or from conditions unrelated to the hypertension.

Hypertrophy without notable dilatation of the left ventricle in essential hypertension is much more often encountered clinically. A large contingent of such patients nowadays is that in which the hypertension is discovered through an insurance or health examination though they have never had any symptoms. They are seen more often in private and dispensary practice than in the hospital wards. Hypertrophy without dilatation is not uncommonly met with in those hypertensive patients who have suffered hemiplegia or other motor disability which curtails their physical activities, as well as in relatively young hypertensive individuals who have headaches and other non cardiac complaints and are apparently early in the disease.

As long as the left ventricle is able to master the hypertension by hypertrophy without dilating notably, there are few if any cardiac symptoms unless coronary artery disease results in manifestations of angina pectoris. Occasionally the patient complains of a feeling of fulness in the cardiac region or of consciousness of the heart's action, but it is doubtful whether these are due to the hypertrophy. This stage of unimpaired cardiac efficiency in essential hypertension may last for many years or even decades. During this period the patient may be capable of very hard physical work. Thus I was acquainted with a man who had a systolic blood pressure of about 220 mm. for fifteen years but nevertheless performed the hard work of a foreman in a railroad yard without difficulty during all this period.

In rare instances of essential hypertension the heart copes successfully with the elevated blood pressure for a considerable time despite the absence of hypertrophy. In some of Aubertin's[32] cases of this variety the heart weighed less than 300 grams.

that the average levels reached in each of these tests in a series of patients corresponded closely to the average maximum routine measurements during the stay in the hospital.

Other Vascular Reactions.—Kauffmann[2] finds that in some though not all individuals with essential hypertension heat causes arteriolar constriction instead of the normal dilatation. In these patients the fingers became pale when immersed in hot water and the blood pressure rose in a hot room. The hypertensive patients with this paradoxical vascular reaction displayed a marked aversion to hot weather during which they *felt poorly*. This behavior is the reverse of that of patients with glomerulonephritis who generally feel better in the warmth. Westphal[8] observed that while in normals the application of the blood pressure cuff for one minute is followed by reactive dilatation of the capillaries of the nail fold seen through the microscope, in most patients with essential hypertension there is an inverse reaction, *i.e.*, constriction.

The vascular reactions in essential hypertension were studied plethysmographically by Iran *et al.*[1] They found that vascular reactions greater than in normals were produced by deep inspiration, the application of cold and hot water, pressure on the eyeball and carotid sinus, and the injection of epinephrine. From these findings they conclude that the sympathetic nervous system is hyperexcitable in hypertensive patients.

The subject of normal vascular reactions in essential hypertension would seem to be of importance and well worthy of further study. I am not aware that any of the observations cited in the preceding two paragraphs have been verified.

The *physical signs* of arterial hypertension have been described on page 271.

THE HEART IN ESSENTIAL HYPERTENSION

The heart of the patient with essential hypertension is confronted by two sources of danger: increased work due to high blood pressure and impairment of blood supply resulting from the coronary arteriosclerosis that almost inevitably develops. Despite these handicaps there are many cases of essential hypertension in which the hypertrophied heart muscle copes adequately with the increased work confronting it, and at no time during the long or short course of the disease are there complaints referable to the heart. However, it is decidedly more common that cardiac symptoms make their appearance sooner or later. In fact, very many individuals with essential hypertension present a clinical picture that is completely dominated by the manifestations of disease of the heart from beginning to end; they are "cardiacs." The cardiac manifestations of essential hypertension, apart from the terminal complication of uremic pericarditis in the malignant phase, consist in heart failure and angina pectoris. In an individual not aware of high blood pressure, the first intimation of disease may be a paroxysm of cardiac asthma or sudden death from myocardial infarction. Or only after decades of high blood pressure with hard labor or repeated pregnancies does the heart begin to weaken or anginal pains appear. In the end, a majority of patients with essential hypertension

exceptional instances in which hypertension has been present for several years and yet the heart looks small presumably the patient originally had a very small drop heart One must be careful not to interpret as cardiac enlargement the transverse position of the heart that often results from obesity with a high diaphragm or a large subpericardial fat pad near the apex One reason why early hypertrophy can not be demonstrated radiologically is revealed by the studies of Kirch (page 278) which showed that left ventricular hypertrophy in hypertension is initiated in the terminal portion of the outflow tract subjacent to the aortic valve this portion of the left ventricle does not reach the borders of the heart in the antero-posterior position and is also difficult to outline clearly in the oblique or lateral positions When the hypertrophy progresses to involve the apical portion of the outflow tract and then the inflow tract there is often a rounding of the apex and an increase in the convexity of the ventricular segment of the left border of the heart This may result in a rather characteristic elliptic outline of the left ventricular border with elevation of the left most point above the diaphragm The rounding is generally best visualized during inspiration when the descent of the diaphragm exposes to view a longer sector of or the complete left border But when this rounding of the ventricular segment of the left border is pronounced there is probably already some dilatation The pulsations as seen fluoroscopically are of smaller amplitude than in the left ventricular hypertrophy of aortic regurgitation Evidences of elongation and dilatation of the arch of the aorta are common in hypertensives Sometimes however post mortem examination does not corroborate the dilatation indicated by fluoroscopic examination (dynamic dilatation) even though when such a discrepancy occurs it is not as pronounced as in aortic regurgitation

THE ELECTROCARDIOGRAM —While there are many patients with essential hypertension of considerable severity and duration in whom the electrocardiogram is normal in a larger number the tracing reveals evidences of the left ventricular hypertrophy that is always present In fact it appears that electrocardiography is sometimes a more sensitive indicator of left ventricular hypertrophy than is radiography although either may be positive when the other is unrevealing In 100 electrocardiograms of patients with essential hypertension subsequently submitted to sympathectomy Evans[35] *et al* found 41 normal In my office practice the majority of patients with essential hypertension detected incidentally and without symptoms have normal electrocardiograms for their age and body type but with symptomatology from any organ the percentage with electrocardiographic abnormalities increases The large majority of patients with symptoms actually correlated with essential hypertension have abnormal electrocardiogram The electrocardiographic picture in essential hypertension includes features due to the body build to the hypertrophy first of the left ventricle and then of other chambers and to coronary arteriosclerosis

1 *Left Axis Deviation* —Master[4] found left axis deviation in 74 per cent of 152 hypertensives The presence of left axis deviation in most patients with essential hypertension is due not only to hypertrophy of the left ventricle but also to the fact that most often they are of sthenic bodily

EVIDENCE OF CARDIAC HYPERTROPHY —The direct objective evidences of cardiac hypertrophy without dilatation are also not striking It is generally agreed that hypertrophy of the myocardium does not in itself enlarge the cardiac area sufficiently to render the enlargement demonstrable as a result of displacement of the apex beat downward or to the left Most clinicians consider the only fairly reliable direct physical sign of hypertrophy of the left ventricle to be the heaving apex beat, as first described by Traube [32] By a heaving apex beat is meant one which lifts the palpating finger with abnormally great force It may be of small amplitude and is not to be confused with a merely prominent apex beat of large amplitude which is not evidence of hypertrophy but may occur in dilatation in the overacting heart of Graves disease or neuro circulatory asthenia, in retraction of the left lung and in many other conditions whether or not hypertrophy is present But the heaving apex beat is by no means a constant finding in cardiac hypertrophy due to arterial hypertension at times especially when there is pulmonary emphysema (H A Derow) one is unable to palpate the apex beat at all despite extreme hypertension of long duration and no evidence of myocardial insufficiency

Nor does percussion reveal definite enlargement of the heart to either left or right Increase in retromanubrial dulness may result from dilatation and elongation of the aorta with consequent wider approximation of the vessel to the anterior chest wall

The first apical sound of the hypertrophic heart is often though not always loud and booming and may seem abnormally prolonged Not uncommonly the first sound is split but it is to be remembered that slight splitting is not uncommon in perfectly healthy individuals The accentuation and other changes in the aortic second sound have already been described (page 272) Systolic murmurs at the apex and base are not uncommon sometimes they arise from atherosclerotic changes in the valves and aorta Far less often the latter produce a regurgitant murmur A diastolic murmur akin to that of organic aortic insufficiency was long ago observed in hypertensive patients by Gibson[33] and Kahler [34] in 3 of the latter's cases necropsy revealed no aortic insufficiency so the murmur must have been 'functional Such functional diastolic murmurs are however apparently rare in hypertension though perhaps not as rare as is generally thought I have heard evanescent diastolic murmurs in the aortic area in several cases of essential hypertension with uremia and in at least 2 of these necropsy disclosed no organic leak The pathogenesis of these diastolic murmurs is not obvious they are perhaps due to a combination of dilatation of the terminal portion of the outflow tract of the left ventricle and stretching of the aortic ring by the high aortic pressure

X RAY FINDINGS —The radiographic examination most often does not furnish unequivocal evidence of left ventricular hypertrophy as long as significant dilatation is absent—so called concentric hypertrophy While the teleoroentgenogram or orthodiagram generally shows that the left transverse diameter is above the average it does not exceed the upper limit of normal in the absence of dilatation It is to be emphasized that careful *x ray examination of the heart may reveal no enlargement or alteration in contour despite hypertension of even five years known duration* There are

3 *Changes in the RS T Segment and T Wave* — Master observed that the T wave is often inverted in the first lead and sometimes also in the second lead in patients with essential hypertension Barnes and Whitten[a] showed that in all conditions in which the left ventricle is under strain (they first used the term left ventricular strain) the T wave may be inverted in the first and perhaps also the second lead while in right ventricular strain these inversions affect the second and third leads The full blown electrocardiographic picture of left ventricular strain in essential hypertension includes a depressed RS-T junction a depressed RS-T segment which is convex upward and an inverted T wave in the first and perhaps also the second lead These findings are usually but not always accompanied by a reciprocally elevated RS-T segment and upright T wave in the third lead The usually depressed RS-T junction in the first lead in left ventricular strain is an important help in differentiation from T wave inversion due to myocardial infarction in which the junction is initially elevated and does not descend below the isoelectric level

By studying the standard limb augmented unipolar limb and precordial leads Sokolow and Lyon elicited abnormal RS-T or T changes in 136 of 147 patients with left ventricular hypertrophy (90 per cent hypertensive) As Master Wilson *et al* and these investigators point out the segmental and T wave changes in hypertension are greatly influenced by the position of the heart In the large majority of hypertensives the heart is horizontal or semihorizontal so that the left ventricular potentials are directed toward the left arm and here the RS-T and T changes are seen in the first (and perhaps the second) lead aVL and V_5 to V_6 On the other hand in the much less frequent instances in which hypertension affects an individual with a vertical heart the potential changes in the left ventricle are directed toward the left leg with the result that the RS-T and T alterations are found in lead aVF and the second and third leads and there may be right axis deviation I have several times known inversion of the T wave in the second and third leads in a hypertensive patient with a vertical heart to be misinterpreted as indicative of old posterior infarction

There is no constancy about the order of appearance of the RS-T and T changes in essential hypertension either depression of the RS-T segment or lowering of the T wave may precede or they may develop concomitantly Since they observed no depression of the RS-T segment in the first lead in 460 normals with left axis deviation Gubner and Ungerleider regard an RS-T depression of as little as 0 5 mm in the first lead in a hypertensive with left axis deviation as significant of left ventricular hypertrophy They similarly found that lowering of T_1 to less than 1 mm does not occur in normals with left axis deviation and therefore consider this also suggestive of left ventricular hypertrophy in hypertensives The RS-T and T changes in hypertension may be first evident in the standard the left precordial or the augmented unipolar limb leads V_4 to V_6 are probably most often earliest to reveal them

The pathogenesis of the RS-T and T changes in essential hypertension has not been entirely elucidated It is correlated with left ventricular strain and hypertrophy for the same electrocardiographic pattern as that seen in hypertension occurs in aortic valvular disease Post mortem exami

habitus and frequently obese, with a resultant transverse position of the heart. The importance of body build for the production of left axis deviation is shown by Gubner and Ungerleider's[37] finding that its incidence varies *pari passu* with the percentage variation of the body weight from the average. In stocky or obese individuals left axis deviation is the rule even though the left ventricle is not hypertrophied and the blood pressure normal, especially in the elderly. Left axis deviation is often absent or the electrical axis even rotated to the right, in slender individuals with essential hypertension despite marked left ventricular enlargement. In the later stages of cardiac insufficiency in essential hypertension enlargement of the right side of the heart may cause the disappearance of left axis deviation.

2. *High Voltage and Other Changes in the QRS Complex.*—High amplitude of the QRS is a common and important, though not constant, manifestation of left ventricular hypertrophy in essential hypertension. It may antedate all other changes in the electrocardiogram. Gubner and Ungerleider found that whereas the sum of R_1 and S_3 is less than 2.2 millivolts in 95 per cent of normals with left axis deviation, this voltage is exceeded in 67 per cent of individuals with left ventricular hypertrophy. High voltage is indicative of left ventricular hypertrophy only in association with left axis deviation, for in the absence of the latter it is often found normally, especially in the slender. High voltage of the QRS is often observed during the stage of concentric hypertrophy and is probably a manifestation of the increased mass of the myocardium of the left ventricle (*cf.* Wilson[38] *et al.* and Lipman and Massie[39] for the factors possibly involved). However Robb and Robb[40] found that increased voltage occurs in rabbits as a result of acute left ventricular strain before hypertrophy could develop.

In the precordial leads, the most common finding in the left ventricular hypertrophy of essential hypertension is a low or absent R and deep S in V_1 and V_2 and a tall R in V_5 and V_6. Sokolow and Lyon[41] found that the sum of the total left ventricular potentials (S in V_1 plus R in V_5 or V_6) rarely exceeded 30 mm. in health but was greater than this in 49 per cent of patients with left ventricular hypertrophy.

The duration of QRS may be increased to 0.12 seconds in left ventricular hypertrophy in the absence of the electrocardiographic pattern of bundle branch block. Sokolow and Lyon found a QRS of 0.11 or 0.12 second in 18 of 147 patients with left ventricular hypertrophy. Wilson and his associates pointed out that in ventricular hypertrophy the time required for passage of the impulse to the epicardium may be prolonged. Sokolow and Lyon found this ventricular activation time as measured from the onset of QRS to the peak of R was prolonged above the normal in V_5 or V_6 in 58 per cent of their patients with left ventricular hypertrophy. Kossmann[42] points out that if the peak of the R wave is more than 0.03 later than the onset of QRS in V_5 than in V_1, it suggests preponderant hypertrophy of the left ventricle.

Q waves of modest size in relation to the R waves are common in left ventricular hypertrophy in the leads toward which the left ventricular potentials are directed. Wilson *et al.* observed them in V_5 and V_6 in more than half and Sokolow and Lyons in about one-third of their cases. It should be remembered that Q waves may be found normally in these leads

THE BALLISTOCARDIOGRAM.—Chesky[50] *et al.* studied the ballistocardiogram in 50 hypertensive patients. Abnormal tracings were obtained in 38, including nine with normal electrocardiograms. As yet ballistocardiographic changes specifically correlated with hypertension have not been differentiated.

CIRCULATORY MEASUREMENTS in essential hypertension are discussed in Chapter 10.

Heart Failure in Essential Hypertension.—*Sooner or later* cardiac insufficiency appears in most patients with essential hypertension. Sometimes the symptoms of heart failure are the initial subjective manifestations, though in such cases examination usually indicates that asymptomatic hypertension had existed for years before. In other patients heart failure appears, if at all, only after years or decades of known high blood pressure. Such heart failure is justifiably termed *decompensation*, for it occurs after the left ventricle had previously compensated by hypertrophy and perhaps other mechanisms for the increased work imposed by the high aortic pressure. The problem of why the heart finally gives way before the hypertension after successfully coping with it for years is of great importance and one about which much remains to be learned. Even at the necropsy of a hypertensive patient who has succumbed to heart failure the judicious observer is often unable to vouchsafe with assurance why the heart failed.

One factor that is probably of primary significance in the pathogenesis of most instances of heart failure in hypertension is *progressive insufficiency of the blood supply to the left ventricle*. This chamber performs increased work to cope with the increased peripheral resistance and hypertrophies in consequence. The bigger muscle mass performing the greater work doubtless requires a more ample blood supply than does a left ventricle of normal size carrying on the usual work. This is all the more likely in the light of the evidence assembled by Wearn[51] that even the normal heart in the resting organism utilizes almost all the oxygen in the arterial blood, leaving but little in the coronary venous blood. And at the same time that the heart hypertrophies, coronary arteriosclerosis develops in a high proportion of the cases. In the large majority of hypertensive patients succumbing to heart failure, well marked coronary arteriosclerosis is found at necropsy.

It seems probable that the very hypertrophy which serves to maintain cardiac compensation in hypertension itself plays a fundamental role in the ultimate failure of the heart. For the increased muscle mass calls for *corresponding* augmentation of blood supply, and even moderate sclerotic changes in the coronary arteries, *per se* not of great significance, may militate against this. But even more significant for the genesis of failure of the hypertensive heart would seem to be the altered quantitative relationships between the myocardial mass and the surface area of the capillaries demonstrated by the important investigations of Wearn. He found that in both the normal adult and the hypertrophied heart there is approximately *one* capillary per muscle fiber. But since each muscle fiber in the hypertrophied heart is thicker, the "concentration" of capillaries falls. Wearn found that *for each* cubic centimeter of myocardium the normal adult heart contains 1.184 square centimeters of capillary surface area while

nation may reveal no disease of the coronary arteries or histological changes other than hypertrophy. Whatever the mechanism of the RS-T and T changes, it is reversible, for after sympathectomy the RS-T segment may rise and the inverted T wave again becomes upright. Yet to be explained is that this may occur even though the blood pressure changes little. Normalization of the RS-T and T changes of hypertension has also been observed as a result of sodium restriction (Bryant and Blecha[44]) or the administration of large doses of potassium (Sharpey-Schafer,[45] Bryant[46]). Perhaps the most probable explanation of the electrocardiographic picture in question is that it is due to relative ischemia of the left ventricle, which in many instances results more from increase in muscle mass than decrease in coronary flow. This explanation equates the pathogenetic mechanism of the electrocardiographic changes with that which probably ultimately causes the failure of the hypertrophied ventricle (page 773). Gubner and Ungerleider point out that the ischemia of coronary insufficiency is most apt to affect the subendocardial region of the left ventricle, where intramyocardial pressure is highest, and the RS-T and T changes of ventricular hypertrophy have many features in common with those resulting from coronary insufficiency. For these reasons they believe that the RS-T and T changes in left ventricular hypertrophy may result from relative ischemia of the subendocardial portions of the left ventricle. Boyer and Hewitt[47] regard their vector studies as opposed to the ischemia theory. They interpret their analysis of the vectors as indicating that the inversion of the T wave in hypertension is secondary to increase in the area beneath the QRS as projected on the frontal plane, which they regard as the primary change, perhaps augmented by decrease in the magnitude of the ventricular gradient. On the basis of these observations Boyer and Hewitt question the theory that the T wave inversion of left ventricular hypertrophy is due to ischemia and believe that both the QRS and the T changes may be due to changes in the rotation and position of the heart. To the writer, however, the predominant weight of evidence seems highly suggestive that the RS-T and T changes of left ventricular hypertrophy are due to a metabolic alteration in the heart muscle of ischemic origin; this conception accords well with the fact that ultimately electrocardiographic changes—notably incomplete bundle branch or arborization block—suggestive of damage to the subendocardial myocardium develop in a high proportion of the cases, and anatomical examination reveals patchy fibrosis.

4. *Electrocardiographic Changes Due to Coronary Arteriosclerosis and Thrombosis.*—At any stage of essential hypertension electrocardiographic changes due to coronary artery disease may develop. In evaluating the electrocardiogram of a hypertensive patient it is always necessary, though often difficult, to differentiate between the changes due to ventricular hypertrophy or shift in the position of the heart and those resulting from coronary narrowing.

For discussions of the results of *spatial vector electrocardiography* in the hypertrophied heart, the reader is referred to the monographs of Grishman and Scherlis[48] and Estes and Grant.[49] The vector method of electrocardiographic interpretation promises to add to understanding of the hypertensive heart.

or other symptoms of heart failure to which little attention has been paid. Among the circumstances which may thus bring hitherto disregarded cardiac weakness to the attention of patients are emotional upsets, lifting heavy weights, climbing stairs, ingesting a heavy meal, and coitus. Acute left ventricular failure with pulmonary *edema* may follow any of these in a patient who previously felt well. But it is to be emphasized that these acute precipitants merely bring to the surface symptomatically latent heart failure by increasing the work of a left ventricle the functional reserve of which had already been narrowed.

3. *Infections.*—On rare occasions an upper respiratory, pulmonary or other infection in a previously well compensated individual with hypertension is followed by heart failure. This may occur during the febrile period or become manifest only after the patient leaves bed. In my experience the number of instances of heart failure in hypertension which have been definitely precipitated by an intercurrent infection has been very small. Even before the days of antibiotics hypertensives usually passed through severe infections such as lobar pneumonia or typhoid fever without developing heart failure; peripheral circulatory failure was a greater risk. Bronchopneumonia is much more often a *consequence* of left heart failure, usually through the intermediacy of pulmonary infarction, than it is a *cause* of cardiac insufficiency.

4. *Superelevation of the Blood Pressure.*—There is no close correlation between the height of the blood pressure in essential hypertension and the liability to heart failure. In relatively young individuals in whom essential hypertension enters the malignant phase, the arterial pressure, especially the diastolic, is usually very high, and yet they almost always succumb to renal insufficiency with the cardiac manifestations in the background of the clinical picture until the last days. Especially in middle-aged women just past the menopause it is not uncommon to observe systolic pressure over 200 and diastolic pressure over 130 mm. for several years with little cardiac enlargement and no evidence of cardiac insufficiency except on considerable exertion. On the other hand, heart failure may develop with a blood pressure which has not exceeded 170/100 mm.; in such cases the failure is presumably predominantly the result of coronary arteriosclerosis. In exceptional cases with widely fluctuating blood pressure an abrupt and marked rise of blood pressure seems on rare occasions to precipitate acute left ventricular failure. This sequence is seen in classical form in true paroxysmal hypertension due to pheochromocytoma. That most instances of acute left ventricular failure with pulmonary edema in essential hypertension are precipitated by superelevation of the blood pressure has not been proved; most of the attacks occur at night and are then due to increased venous return in the recumbent posture. In this connection it should be borne in mind that left ventricular failure with pulmonary edema often causes a secondary rise in blood pressure, probably as a result of asphyxia. When overexertion induces left ventricular failure in hypertension, the increased venous return to the heart is probably a more significant pathogenetic factor than the change in blood pressure; indeed, while severe physical exercise results in elevation of the systolic pressure, the diastolic pressure most often is either unchanged or falls.

the hypertrophied heart averages only 623 square centimeters It is thus evident that gaseous diffusion and other metabolic exchanges are handicapped in the hypertrophied heart because they must take place over a longer distance Further support for the conception that the blood supply to the hypertensive heart does not keep pace with the hypertrophy is afforded by the finding of Gross and Spark[5] that the average number of arterioles per low power field diminishes in inverse proportion to the weight of the heart

Progressive insufficiency of the metabolic exchanges between blood and heart muscle due to the enlargement of the muscle fibers may alone cause heart failure in some hypertensive patients But in other cases, the actual appearance of clinical symptoms of heart failure is precipitated by various factors which accentuate the disproportion between the functional capacity of the left ventricle and the demands made on it Among these are the following

1 *Clinically Manifest Coronary Arteriosclerosis* —In the foregoing, we have seen that coronary arteriosclerosis is probably one of the underlying pathogenetic factors in most instances of heart failure in essential hypertension Sometimes however, the coronary sclerosis produces neither clinical symptoms nor electrocardiographic changes And exceptionally, even at necropsy, the sclerosis may compromise the lumens of the coronary arteries so little that one would attribute slight significance to it, were there not the greatly hypertrophied left ventricle with its need of an abnormally large blood supply But in other cases the coronary arteriosclerosis is so severe that it is obviously the principal and immediate cause of the heart failure The latter may be initiated suddenly by major coronary thrombosis or by a change in rhythm Or the coronary artery disease may be revealed by either anginal pains or electrocardiographic evidences of myocardial damage which in long-standing hypertension one is generally safe in attributing to narrowing of the coronary arteries Averbuck[193] found that severe coronary arteriosclerosis was present in necropsy in 85 per cent of patients with essential hypertension who had heart failure, but in only 10 per cent of hypertensive individuals without cardiac insufficiency In a large majority of the necropsies that I have seen on hypertensive patients succumbing to heart failure actual coronary occlusions or extreme narrowing of coronary branches with focal scarring of the myocardium have been present Such a manifestly coronary origin of heart failure in hypertension appears to be more common in the male In individuals with both hypertension and diabetes coronary arteriosclerosis is generally very severe and is most often the manifest cause of heart failure Similar preponderance of the coronary element in the causation of heart failure is more common in the very old than in the relatively young individual with hypertension In the heart failure that is not uncommon, in addition to renal insufficiency in the terminal stages of the malignant phase of essential hypertension the coronary element is usually absent or slight

2 *Overexertion* —Not uncommonly, patients with hypertension attribute their symptoms of heart failure to some physical or emotional stress Most often, careful interrogation elicits antecedent dyspnea on exertion

aided heart failure may produce functional emphysema. The engorgement of the lungs erects the vessels and interferes with expiratory collapse and thus tends to maintain the lungs in an average position closer to that of inspiration than in health. Emphysema may be either cause or consequence of heart failure in essential hypertension.

Onset.—Exertional or paroxysmal shortness of breath most often heralds the weakening of the heart in essential hypertension. The development of dyspnea is sometimes sudden but much more often insidious. Even when the patient states that dyspnea set in abruptly during exertion or sleep, questioning often elicits progressive diminution in exercise tolerance for a considerable period before. If the dyspnea is actually of sudden onset, especially careful search should be made for coronary insufficiency or myocardial infarction. Nocturnal cough regarded as bronchitis, palpitation and a feeling of weight in the region of the heart are other frequent early complaints. Obese persons often delay visiting their physician because they attribute these symptoms to adiposity. Abdominal pain, distention and flatulence, perhaps due to congestion of the liver and other abdominal viscera, are occasional early manifestations of weakening of the hypertensive heart; the patient may think his symptoms are due to primary gastric or intestinal trouble and often attempts to treat them with cathartics or antacids. Nocturia or inability to sleep on the left side are common complaints as the heart becomes inadequate; older men often blame the former on prostatism. The early symptoms of heart failure in essential hypertension are often commingled with anginal manifestations of coronary insufficiency, and the physician may be hard put to differentiate them.

The Stage of Left Ventricular Failure.—Heart failure in essential hypertension most often sets in with symptoms due to engorgement of the pulmonary circuit without accompanying evidences of stasis in the tributaries of the venae cavae. This clinical picture is now generally known as left ventricular failure. It was long ago described by Gallavardin[33] and other French clinicians as the stage of *isolated insufficiency of the left ventricle*. In my experience such a stage has been clearly discernible in the anamnesis of a large majority of patients with cardiac failure resulting from essential hypertension. Uncomplicated left ventricular failure may last for years in patients with essential hypertension and recur over a decade. In others, symptoms of failure of both sides of the heart seem to be commingled from the onset of cardiac weakness. When encountered, however, the syndrome of uncomplicated left ventricular failure in essential hypertension presents a very striking clinical picture, the main features of which, in a typical case, are as follows:

a. Dyspnea on exertion and, what is more characteristic when present, attacks of cardiac asthma. The dyspnea is often accompanied by orthopnea.

b. Absence of peripheral venous stasis and its consequences.

c. Dilatation of the left ventricle.

d. Evidences of stasis in the pulmonary circuit, though this may be difficult to demonstrate by the usual clinical means.

e. Fall in blood pressure, but this is far from constant (see page 788).

5 *Obesity* —Individuals with essential hypertension are often obese, and when the adiposity is marked it may play a role in the production of cardiac insufficiency. The excessive body weight of course increases the work of the heart, especially during physical exertion. Also, the upward displacement of the diaphragm due to enlargement of the omental and other fat depots in the abdomen in most obese persons places the heart in a more transverse position in which it may work at a mechanical disadvantage. Furthermore, in extremely obese individuals there may be extensive deposition of fat under the epicardium with infiltration between the myocardial fibers down to the endocardium (so-called *lipomatosis cordis*). Not uncommonly, symptoms of heart failure in obese persons with high blood pressure are alleviated when body weight is reduced.

6 *Complicating Valvular Lesions* — Arteriosclerotic changes in the mitral and aortic valves are common in long standing essential hypertension. Usually they are merely post-mortem discoveries though they may produce systolic murmurs. Less often arteriosclerotic changes produce aortic diastolic murmurs. Such arteriosclerotic valvular lesions seem to play little part in the pathogenesis of heart failure in essential hypertension.

Essential hypertension develops frequently in middle aged women with rheumatic mitral stenosis (page 791). The combination of arterial hypertension and mitral stenosis does not seem especially unfavorable as regards the production of heart failure. I have seen many cases in which they have co-existed for years without heart failure. Indeed it seems plausible that the narrowing of the mitral ostium tends to spare the left ventricle. But patients with both mitral stenosis and essential hypertension are much more apt to develop auricular fibrillation than those with only high blood pressure. When heart failure is initiated with auricular fibrillation in an individual with high blood pressure the possibility of occult mitral stenosis should be borne in mind, even though characteristic murmurs are not audible during the period of rapid heart action.

The association of essential hypertension with aortic regurgitation of rheumatic or syphilitic etiology is not as common as with mitral stenosis (except in population groups with a high incidence of syphilis) but is not rare. Of course the purely systolic hypertension of aortic regurgitation must not be confused with essential hypertension. While some of the cases do well for a considerable time, those due to syphilis are especially apt to develop rapidly progressive heart failure and sudden death is common, most often as a result of stenosis of the coronary ostia.

7 *Emphysema* — This is a frequent complication in older hypertensives and often seems to play a part in the production of heart failure. The clinical picture in the late phases may be predominantly that of cor pulmonale. This occurs in that stage in which, as a result of weakening of the left heart, the pressures in the pulmonary circuit have risen and the right ventricle has hypertrophied; the development of emphysema naturally throws a further strain on it. In fact it is not uncommon in patients with essential hypertension and emphysema that the latter seems to be the more important factor in causing the cardiac breakdown. In two such cases the right ventricle was found at necropsy to be considerably more hypertrophied and dilated than the left. It should be borne in mind that left

paired or relatively less affected than that of the left ventricle so that there occurs an increase of tension in the pulmonary circuit This often, if not always leads to the production of pulmonary edema At least in some attacks of cardiac asthma in which neither the expectoration nor the physician s examination afford evidence of pulmonary edema the latter may be disclosed by transitory cloudiness of the lung field in the *x* ray picture In fact the frequent occurrence of pulmonary edema in the cardiac asthma of hypertension and aortic insufficiency forms one of the strongest supports of the Welch Cohnheim theory of pulmonary edema which attributes the transudation into the alveoli to a relative predominance of the right ventricle over the left with consequent increase in pressure in the pulmonary capillaries

The mechanism through which left ventricular failure leads to paroxysmal dyspnea has been the object of much investigation While Hoover[59] Wassermann[60] and others believed that the dyspnea is due to a decrease in blood flow to the brain the investigations of Harrison[61] have shown that left ventricular failure produces cardiac asthma through the intermediacy of pulmonary engorgement and consequent decrease in vital capacity As Harrison s studies show the actual paroxysm is precipitated by intensification of the pulmonary engorgement which may become so marked as to produce pulmonary edema In the production of the pulmonary engorgement combination of the recumbent position and sleep appear to be of fundamental importance The recumbent position produces a shift of blood from the abdomen and lower extremities to the lung with a weakened left ventricle the result is pulmonary engorgement and consequent decrease in vital capacity And the diminished sensitivity of the nervous system during sleep presumably allows this engorgement to attain a higher degree than would otherwise be the case Among the other factors which may participate in the nocturnal intensification of pulmonary engorgement are dreams cough and the resorption of manifest or occult edema when recumbent The last mentioned mechanism—increase in blood volume and venous return to the heart as a result of resorption of increased intercellular fluid in the lower extremities after change from the erect to the recumbent posture—is probably the most important factor in many attacks of cardiac asthma This conception is supported by the observations of Perera and Berliner[62] who found in patients with nocturnal cardiac asthma that the plasma protein concentration is lowered after several hours in bed and then again rises ten or fifteen minutes after the onset of the paroxysm when the patient has sat up and gasped for some time—defensive acts which tend to terminate the attack. It is probably through lessening the volume of extracellular fluid and thus decreasing the amount resorbed at night that sodium restriction and mercurial diuresis often prevents the attacks

Orthopnea is often a striking characteristic of the breathlessness of left sided heart failure This is not surprising for there is good evidence to show that orthopnea is a manifestation of pulmonary engorgement

A paroxysm of cardiac asthma may occur at any time of the night but is most common in the first hours of sleep The patient may have felt well before retiring or he may have been dyspneic He awakens sud-

1 Dyspnea on Exertion and Cardiac Asthma —Dyspnea on exertion is the complaint which most often brings the patient with a failing hypertensive heart to the doctor It may be noticed only when performing some such task as climbing stairs or walking against the wind, or after a heavy meal The dyspnea may be very intense despite the complete or almost complete absence of signs of peripheral venous stasis Orthopnea is common in left ventricular failure and may be the initial complaint Patients, even when physicians, use many analogies to describe the purely subjective sensation of dyspnea, and when the description is atypical it may be difficult to decide whether the thoracic, cervical or epigastric discomfort induced by exertion is dyspnea or angina pectoris i e whether the symptom is respiratory embarrassment due to weakness of the left ventricle or the pain of myocardial ischemia produced by the coronary arteriosclerosis so common in essential hypertension The differentiation is an important one especially for rational therapy but unfortunately can not invariably be made with certainty Doubtless dyspnea and angina pectoris are often combined to form a complex sensation

Cardiac Asthma —The dyspnea of effort may be accompanied by attacks of cardiac asthma Or what is not rare cardiac asthma is the only symptom pointing to insufficiency of the left ventricle the dyspnea on exertion being so slight that a patient leading a sedentary life does not complain of it and its existence is elicited only after careful questioning if at all Rarely a paroxysm of cardiac asthma is the first symptom which leads the patient with essential hypertension to seek medical aid Failure to measure the blood pressure has resulted in such patients being treated for true bronchial asthma

The term cardiac asthma is applied to paroxysms of dyspnea occurring when the patient is at rest as a rule awakening him from sleep and often accompanied by demonstrable acute edema of the lungs In 94 per cent of Pratt s[64] cases the initial seizure occurred while the patient was quiet in bed Cardiac asthma is a symptom of left ventricular failure This is most often due to hypertension Pratt found that in 18 of 30 patients with cardiac asthma the systolic pressure was abnormally high while in 17 of 23 cases in which he determined the diastolic pressure this was above 100 mm He considers it probable that in some of the patients in whom the blood pressure was within normal limits it had been previously elevated However hypertension is not the only cause of cardiac asthma Typical attacks of cardiac asthma are not uncommon in syphilitic aortitis (9 of Longcope s[65] 63 cases) and coronary artery disease in the former presumably most often when the mouths of the coronary arteries are narrowed They also occur in the left ventricular failure of rheumatic aortic insufficiency particularly when there is marked systolic hypertension Cardiac asthma is extremely rare in pure mitral disease It seems that in most of the cases of essential hypertension in which cardiac asthma occurs there is also well-marked coronary artery disease Hypertensive patients who have never before had cardiac asthma not uncommonly first develop such attacks after renal insufficiency has set in

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